APPENDIX A

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Current Opinion in Pharmacology

Pharmacologic treatment of constipation: what is new?

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Constipation is a common gastrointestinal disease affecting 2–27% of the population in Western hemisphere. Approximately in half of patients the diagnosis of functional constipation is made after having ruled out secondary causes. Treatment of chronic functional constipation primarily addresses education on toilet habits, dietary advice, and patient reassurance. Further therapies are guided according to functional subtype slow-transit constipation, dyssynergic defecation, and constipation-predominant irritable bowel syndrome (IBS-C). Traditionally, the pharmacologic treatment of constipation uses primarily bulking agents and/or laxatives (osmotic or secretory). However, often these therapies do not provide the desired improvement, have a short-lived efficacy and/or are accompanied by side-effects such as bloating and abdominal cramps. Thus, there is a clinical need for new, more potent drugs particularly for patients who are not satisfactorily treated by conventional therapies. This review discusses recent developments in the pharmacologic treatment of chronic constipation including recently FDA-approved lubiprostone, emerging 5-HT receptors modifiers, investigational substances, and probiotics.

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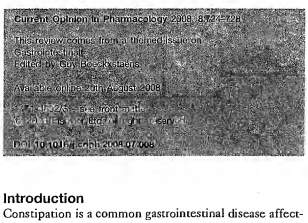

Introduction

Constipation is a common gastrointestinal disease affecting between 2 and 27% of the population in western countries [1–3]. Variances in estimation of prevalence vary greatly due to different definitions of constipation. Females are more frequently affected than males, children more often than adults, the elderly more often than young adults and Caucasian more often than non-Caucasian [4–6]. Approximately in two-thirds of patients constipation begins in adulthood, in one-third during childhood. Frequently reported symptoms are hard stools, infrequent defecation (usually less than three bowel movements per week), excessive straining, incomplete evacuation with or without the use of digital rectal manœuvers, and the use of laxatives. Causes for chronic constipation are often multifactorial: endocrine or metabolic disorders, neurologic disorders (Parkinson disease, multiple sclerosis, spinal lesions, autonomic neuropathy, etc.), psychiatric disorders (depression and eating disorders), pharmacologic agents (opiates, anticholinergics and antidepressants), structural lesions (tumors and anal fissures) and lifestyle factors (dietary, repressed urge to defecate, and immobility) must be excluded as causes of constipation. Independent nonstructural risk factors for constipation include physical inactivity, low income, low education, a history of sexual abuse, and symptoms of depression [7]. In the absence of these causes and comprising at least 50% of patients the diagnosis of functional constipation may be made [8,9]. Functional constipation may be defined as three overlapping subtypes [10,11]: slow-transit constipation, dyssynergic defecation, and constipation-predominant irritable bowel syndrome (IBS-C).

Treatment of chronic constipation addresses primarily education about toilet habits, dietary advice, and patient reassurance. More specific treatments are guided according to functional subtype. Some patients with dyssynergic defecation may benefit from pelvic floor rehabilitation (i.e. biofeedback-training) [12]. Pharmacologic treatment of constipation has been traditionally based on osmotic or secretory laxatives and bulking agents. However, these therapies often fail, may have a short-lived efficacy and induce side-effects such as bloating and abdominal cramps. Thus there is a clinical need for new, more potent drugs particularly for patients that are not satisfactorily treated by conventional therapies.

This review summarizes recent developments in the pharmacologic treatment of chronic constipation focusing on chloride channel activators, selective 5-HT_4 agonists, investigational drugs, and probiotics. We reviewed PubMed-listed publications of the past five years and abstracts presented at the major gastroenterology meetings (AGA-DDW, UEGW).

Chloride channel activators

Lubiprostone is the latest agent to receive FDA approval for the treatment of adult patients with chronic idiopathic constipation [13,14]. This bicyclic functional fatty acid acts as a selective chloride channel (ClC-2) activator in the apical membrane of the gastrointestinal epithelium to

increase intestinal chloride secretion [15] and thereby intraluminal fluid collection in the gut. This facilitates transit in the intestine and eases stool passage.

The efficacy of lubiprostone in the treatment of patients with chronic constipation has been shown in various trials. In a well-designed study Johanson and Ueno randomized 129 adult patients with chronic constipation to receive lubiprostone (24, 48, or 72 mcg/day) or placebo for 3 weeks [16•]. Monitoring the frequency of spontaneous bowel movement (SBM) frequency the authors noted a statistically significant ($P < 0.05$) increase in the frequency of SBM (lubiprostone 5.1–6.1 versus placebo 3.8). Patients receiving higher lubiprostone doses (48 mcg/day or 72 mcg/day) had significantly higher SBM rates on the first day of treatment, during the first and second week compared to placebo but the benefits of the highest dose (72 mcg/day) did not lead to meaningful differences compared to the 48 mcg/day dose. Common side-effects included nausea, headache, and diarrhea, the frequency and intensity of side-effects being dose dependent. On the basis of these findings the authors concluded that lubiprostone improves the frequency of SBMs in a dose-dependent manner and according to a risk-benefit assessment lubiprostone 48 mcg/day had the optimal profile.

Following up on this study, the same group reported in January 2008 the results of a large multicenter, double-blind, randomized, placebo-controlled study in 242 patients with chronic constipation treated with either lubiprostone 24 mcg bid or placebo bid for 4 weeks [17••]. The 120 patients receiving lubiprostone reported a greater number of SBMs at week 1 compared with the 122 patients receiving placebo (average SBM/week lubiprostone 5.69 versus placebo 3.46, $P < 0.01$). The frequency of SBMs was greater at weeks 2, 3, and 4 ($P < 0.01$). The promptness in improving defecation frequency was underscored by the percentage of patients having SBM within the first 24 hours (56.7% of patients receiving lubiprostone versus 36.9% of patients receiving placebo; $P < 0.01$). Within 48 hours 80% of lubiprostone-treated patients and 60.7% of placebo-treated patients reported SBMs. The most common treatment-related side-effects were nausea (31.7%) and headache (11.7%). These findings prompted the authors to conclude that treatment with lubiprostone leads to bowel movements in the majority of individuals within 24–48 hours after the initial dose and improves the frequency of bowel movements over a 4-week period.

Lubiprostone was also found to be efficient in treating patients with IBS-C and recently FDA approved for this indication [13]. In a placebo-controlled study Johanson *et al.* randomizing 195 patients with IBS-C to receive lubiprostone 8 mcg bid ($N = 52$), lubiprostone 16 mcg bid ($N = 49$), lubiprostone 24 mcg bid ($N = 46$), or placebo bid ($N = 48$) for three months [18]. Lubiprostone 24 mcg bid and 16 mcg bid doses improved the frequency of SBMs compared to placebo at one month (weekly SBM rate change from baseline lubiprostone 24 mcg bid 3.2 ± 1.4 versus lubiprostone 16 mcg bid 2.1 ± 0.7 versus placebo 0.7 ± 0.4; $P < 0.05$), two months (weekly SBM rate change from baseline lubiprostone 24 mcg bid 2.6 ± 1.2 versus lubiprostone 16 mcg bid 1.7 ± 0.7 versus placebo 0.8 ± 0.4; $P < 0.05$), and three months (weekly SBM rate change from baseline lubiprostone 24 mcg bid 2.5 ± 1.2 versus lubiprostone 16 mcg bid 1.6 ± 0.8 versus placebo 0.5 ± 0.6; $P < 0.05$). The abdominal discomfort/pain scores improved only transiently (at one and two months) and at three months were no different compared to placebo. Adverse reactions (mainly abdominal distension/pain, diarrhea, and nausea) were noted more frequently in patients receiving the active drug compared to placebo (diarrhea lubiprostone 12–27% versus placebo 4%, nausea lubiprostone 18–31% versus placebo 13%). Albeit not reaching significance a trend toward more side-effects with increasing doses of lubiprostone was noted. Reviewing the benefits and adverse events during treatment with lubiprostone the authors concluded that lubiprostone 16 mcg daily is the optimal dose to treat IBS-C patients.

5-HT$_4$ agonists

Tegaserod, a partial agonist at the 5-hydroxy-tryptamin-4 (5-HT$_4$) receptor, was primarily introduced for the treatment of women with IBS-C in 2004. In 2006, the indication of treatment was extended to chronic idiopathic constipation in both men and women below the age of 65. In 2007, after a meta-analysis finding an increased number of cardiovascular events in patients treated with tegaserod the producer (Novartis) withdrew the compound from the market at FDA's request [19].

The tegaserod experience taught important lessons on the role of 5-HT in modulating gastrointestinal motility. The targeted 5-HT$_4$ receptors in the enteric nervous system are presynaptic and facilitate the release of acetylcholine and calcitonin gene related peptide. These compounds stimulate their effector structures that include smooth muscle cells, interstitial cells of Cajal (ICC), and secretory glands [20–24]. 5-HT$_4$ receptor activation initiates the peristaltic reflex, increases fluid secretion in the intestine, and inhibits visceral sensitivity. Hereby it decreases colonic transit time and consecutively improves the number of bowel movements, constipation-related abdominal dyscomfort, and bowel satisfaction [25–27].

On the basis of these novel experiences, more selective 5-HT$_4$ receptor agonists have been investigated. Prucalopride is a highly selective, high-affinity 5-HT$_4$ with enterokinetic effects. In contrast to other 5-HT$_4$ receptor agonists (cisapride, tegaserod, mosapride, and renzapride) it does not interact with 5-HT$_3$ and 5-HT$_{1B}$ receptors and

the hERG channels. This high selectivity is believed to lead to a more favorable risk-benefit profile compared to the other non-selective 5-HT_4 agents. Sloots *et al.* randomized 28 patients with chronic constipation to receive prucalopride 1 mg, prucalopride 2 mg, or placebo in a double-blind, randomized cross-over study [28]. Compared to placebo, prucalopride 1 mg increased ($P < 0.05$) the mean number of spontaneous complete, spontaneous, and all bowel movements per week and decreased the frequency of hard/lumpy stools and the need to strain. Measuring the colon transit time the authors found a decrease ($P = 0.07$) in colonic transit time during treatment with prucalopride (42.8 hours) compared to placebo (54.8 hours). Despite a limited number of patients included in this study these data suggest that prucalopride improves stool frequency and consistency, and may decrease colonic transit times in patients with chronic constipation.

In the same year Emmanuel *et al.* reported the results of a double-blind placebo-controlled study evaluating the effects of prucalopride in 74 women with chronic constipation (stratified into slow and normal transit) [29]. Quantifying the frequency of SBMs, oroccecal transit, visceral sensitivity, and quality of life before and after 4 weeks of treatment with prucalopride 1 mg daily the authors noted an increase in the frequency of SBMs per week (prucalopride 7.6 ± 5.7 versus placebo 5.0 ± 3.6; $P = 0.019$), a reduction in the median [25–75th percentile] time to first stool (prucalopride 3.5 [1.2–23.6] hours versus placebo 24.2 [6.3–69.0] hours; $P < 0.001$) and a decreased number of retained markers (prucalopride 51.2 ± 29.6 versus placebo 61.8 ± 30.2; $P = 0.018$). Compared to placebo, prucalopride increased rectal sensitivity to distension (urge volume, $P = 0.01$) and electrical stimulation ($P = 0.001$), and significantly improved several domains of the Short Form Health Status Survey and the disease-specific quality of life. The results of this study suggest that prucalopride improves gastrointestinal transit and gut sensitivity in constipated patients with both slow and normal transit.

These early results were confirmed this year in a large phase III study in which Camilleri *et al.* randomized 620 patients with severe chronic constipation to receive prucalopride 2 mg, prucalopride 4 mg, or placebo once daily for 12 weeks [30••]. The primary clinical end-point of the study was the proportion of patients with an average of more than three SBMs per week. At the end of the study there was a higher proportion of patients with more than three SBMs per week in the group receiving prucalopride (2 mg — 30.9% and 4 mg — 28.4%) compared ($P < 0.01$) to placebo (12%). The most frequent adverse events were headache (26.6–29.4% prucalopride versus 12.0% placebo) and diarrhea (13.5–18.6% prucalopride versus 5.3% placebo). On the basis of these findings the authors concluded that prucalopride improves bowel function and reduces the frequency/severity of symptoms of severe chronic constipation.

Investigational agents

A number of 5-HT_1 receptor agonists are currently under investigation with the goal to avoid the cardiac side-effects seen with tegaserod.

One candidate is renzapride, a 5-HT_4 receptor agonist and 5-HT_3 receptor antagonist [31]. The effects of renzapride have been documented in patients with chronic constipation and IBS with and without constipation [32,33•,34]: a study by Camilleri *et al.* reported relief of symptoms of constipation by improving stool consistency and a decrease in colonic transit time [34]. Subsequently George *et al.* reported the results of a multicentre, double-blind study in which 510 patients with IBS-C recruited in the primary health care setting were randomized to receive renzapride 1, 2, or 4 mg or placebo [33•]. Although the study's primary endpoint (selfreported reduction in duration and severity of abdominal pain) did not reach statistical significance, a post hoc analysis of data collected in IBS-C female patients receiving renzapride 4 mg daily found a significant proportion of responders (responder rate 12%). The study had a high drop-put rate (38.6%) mostly because of adverse events such as diarrhea, headache, and abdominal pain. Other 5-HT_4 agonists, such as mosapride [35,36] are also under investigation.

Special forms of chronic constipation are opiate-induced constipation and postsurgical ileus. For this indication methylnaltrexone and alvimopan are currently under investigation. Unlike classical opiate antagonists (naloxon and naltrexon) they do not exhibit any impact on central analgesic effects [37,38]. However recent data from patients with chronic functional constipation are discouraging. A lack of efficacy of alvimopan, a peripherally acting mu-opioid receptor antagonist, was demonstrated in the treatment of patients with chronic idiopathic constipation in an 8-week, double-blind trial when compared to placebo [39••]. Negative results were also presented by Foxx-Orenstein when investigating a supportive effect of nonselective opioid antagonist naltrexone in combination with tegaserod in IBS-C patients [40]. Although these compounds have been found useful in the treatment of opioid-induced constipation further studies in nonopioid-dependent patients are warranted before these compounds become of interest for patients with functional chronic constipation.

Another investigational compound is the guanylate cyclase agonist linaclotide, a drug developed for the treatment of functional constipation [41]. In a first phase II trial Andresen *et al.* investigated the effects of oral linaclotide 0.1 mg and linaclotide 1 mg once daily in 36 women with IBS-C [42•]. Linaclotide positively influenced ascending colon emptying half-time (linaclotide 1 mg 7.8 ± 1.7 hours versus placebo 17.0 ± 2.0 hours; $P < 0.01$), overall colon transit over 48 hours (scintigraphic determined geometric center linaclotide 1 mg

4.0 ± 0.2 versus placebo 3.1 ± 0.2; $P = 0.01$) and bowel function including frequency of bowel movements, stool consistency, and ease of passage (evaluated with patient diaries). These effects were dose-dependent and noted only for linaclotide 1 mg.

Neurotrophins are neuronal growth factors that stimulate the development, growth, and function of the nervous system for the potential treatment of neuropathies such as Parkinson Disease [43]. Selective neurotrophins such as neurotrophin-3 (NT-3) have been discussed as potential therapeutic targets in spinal-injury induced constipation, M. Hirschsprung and also functional constipation [44–46]. Till date, published results are limited to one randomized placebo-controlled trial with NT-3 administered subcutaneously. In this study, Parkman *et al.* demonstrated an increase in the frequency of bowel movements (total and spontaneous), constipation-related symptoms, and stool quality in 107 patients receiving 9 mg NT-3 subcutaneously three times per week. However, side-effects were considerable as approximately one-third of patients experienced significant pain at injection site.

Probiotics

Probiotics have been suggested to have favorable effects on gastrointestinal function including suppressing growth of pathogenic bacteria, blocking epithelial attachment by pathogens, enhancing mucosal function, and modulating host immune response [47]. Placebo-controlled data on possible treatment of constipation using probiotics are sparse. De Paula *et al.* evaluated 266 female patients with functional constipation (according to Rome II criteria) that were randomized to receive a yogurt containing a mixture of *Bifidobacterium animalis* (DN-173 010) and prebiotic fructooligosaccharide (FOS) [48] twice a day for 2 weeks or a lacteous dessert. There was a 22% increase in the number of bowel movements per week and a slight increase in stool quality as assessed by the Bristol Stool Questionnaire when compared to placebo. Perception of pain and straining during defecation were reported significantly reduced in the females ingesting the symbiotic yoghurt. In an earlier study Koebnick *et al.* demonstrated a significant improvement in selfreported constipation severity in 70 constipated adults after the ingestion of *L. casei* shirota versus placebo over 4 weeks [49]. A 24% increase in evacuation frequency was observed combining *L. rhamnosis* and *Propionibacterium freudenreichii* versus placebo [50]. However, absolute changes in defecatory and symptoms parameters were small in these studies, making a clinically significant treatment effect uncertain.

Conclusion

Functional constipation is a common gastrointestinal disorder. After tegaserod being withdrawn from the market, the therapeutic armamentarium for functional constipation has been complemented by other agents. The chloride channel activator lupiprostone has recently received FDA approval for chronic constipation and IBS-C. More selective 5-HT_4 receptors agonists and other investigational compounds targeting enteric neurons such as guanylate cyclase agonist, neurotrophins, or endogenous opioids are currently under investigation. The main challenges in developing novel therapies are their clinical safety and efficacy. Like for any other functional disorders, patient selection has a pivotal role in any of the discussed agents and should be carefully examined by manufacturers and drug-licensing institutions.

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Recent concepts in the management of bowel problems after spinal cord injury

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Abstract

Bowel problems after SCI can be debilitating. Colonic inertia as a result of decreased parasympathetic (S2-4) stimulation of the left colon and rectosigmoid seems to be the principal abnormality accounting for DWE. The conventional measures used for decades have poor results in many people. Neostigmine, an anticholinesterase inhibitor, appears to be a more physiological agent for these individuals. The combination of neostigmine + glycopyrrolate infusion has shown encouraging results after intravenous administration and studies are under way to assess the efficacy of neostigmine by other routes.

Introduction

A significant number of individuals with chronic spinal cord injury (chronic SCI) have gastrointestinal (GI) symptoms due to bowel dysfunction [1]. Adequate bowel care is an important part of their management. The intent of this paper is to acquaint physicians with the pathophysiology of bowel problems after SCI and to summarize current concepts in the management of individuals who have sustained such damage.

Magnitude of the problem

According to the most recent data from the National Spinal Cord Injury (NSCI) Database, the prevalence of SCI in the US is approximately 250 000 with 12 000 new cases each year [2]. About 40-50% of injuries to the spinal cord are due to motor vehicle accidents [3]. The severity of the injury determines the outcome and can be classified using the American Spinal Injury Association (ASIA) impairment scale (*Tab. 1*) into five different stages [4]. The economic burden of this problem is with the direct and indirect (loss of income and productivity) annual cost of managing these individuals estimated to be at least $ 4 billion. These costs are especially high since these injuries typically occur in young males (average age of 37.6 years at the time of injury) [5].

SCI results in permanent disability in about 30-40% of cases [1,6-8]. In addition to the physical limitations due to paralysis, bowel and bladder problems are common. In terms of bladder dysfunction, use of intermittent catheterization has significantly reduced the incidence of urinary tract infections and improved the survival rate [9].

As a result, bowel dysfunction has become a more major issue [1,6-8]. To manage this problem effectively, it is first important to understand normal neuromuscular coordination of the colon and the pathophysiological changes which occur after SCI.

Neuromuscular coordination of the colon

Normal colonic and anorectal function is important for the process of defecation. The internal anal sphincter (IAS), an involuntary sphincter, is the continuation of the inner circular muscle layer of the colon. In contrast, the external anal sphincter (EAS) is made up of striated muscle layer and is under voluntary control [10]. Normal function of the EAS is important in preventing premature expulsion of feces and its integrity is a major factor in maintaining continence.

The colon is richly supplied with both autonomic (parasympathetic and sympathetic) and somatic (sensory and motor) innervation (*Fig. 1*) [11]. These different pathways are integrated by higher centers in the brain and spinal cord. The parasympathetic innervation of the colon is responsible for colonic contractions and motility. The right and proximal transverse colon are innervated through the vagus nerve while the left colon and rectum receive input from spinal segments S2-S4

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Received 04.07.2006 Accepted 19.07.2006

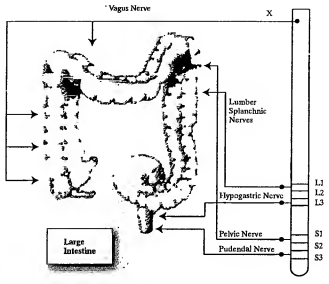


Figure 1. Extrinsic innervation of the large intestine. The vagus nerve (X) innervates the right colon while propulsive activity in the left colon is mediated by the parasympathetic (pelvic) nerves. Sympathetic innervation (L1-3) via the splanchnic nerves and hypogastric nerves is inhibitory. The anal canal is innervated by voluntary efferent motor fibers to the external anal sphincter via the pudendal nerve from the sacral spinal cord (S2-4)

Table 1. American Spinal Injury Association (ASIA) impairment scale

Grade	Description
A	Complete; no sensory or motor function preserved in the sacral segments S4-S5
B	Incomplete; sensory but not motor function preserved below the neurological level and extending through the sacral segment S4-S5
C	Incomplete; motor function preserved below the neurological level; most key muscles have a grade <3
D	Incomplete; motor function preserved below the neurological level; most key muscle have a grade >3
E	Normal motor and sensory function

via pelvic nerve or nervi erigentes [11]. The sympathetic supply originates from the lumbar splanchnic nerves and is the major pathway for carrying the sensations from the colon. The somatic fibers innervating the EAS are derived from the pudendal nerve (S2-S4). These nerves directly innervate the colon and also form Auerbach's and Meissner's plexuses within the muscle layers. Together, these plexi constitute what is termed the enteric nervous system (ENS) [10,11].

The neuromuscular innervation of the colon results in both non propulsive contractions under the control of ENS as well as high amplitude propagating contractions (HAPC) [1]. Various neurotransmitters including acetylcholine, catecholamines, and serotonin have been shown to regulate colonic motility. However, the principal autonomic neurotransmitter is acetylcholine [12].

Pathophysiological changes after SCI

Prolonged mouth to cecum transit time (MCTT) has been shown in individuals with quadriplegia using radio-opaque markers [13,14]. Segmental evaluation has also shown pro-

Figure 2. Effect of food ingestion on the motility index (mm Hg). The motility index increased significantly in both SCI ($p<0.01$) and SI ($p<0.02$) subjects after meal ingestion, but to a lesser extent in the latter

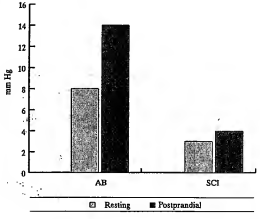


Figure 3. Effect of food ingestion on the no. of waves per hour. There was a significant increase in the number of waves seen in SCI ($p<0.008$) as well as SI ($p<0.005$) subjects after meal ingestion

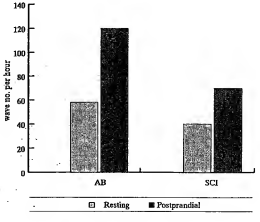


Figure 4. The effect of food ingestion on the motility index shows regional variation in the SCI group. The increase in motility index (mm Hg) was only significant in the descending colon ($p < 0.03$) and not the rectosigmoid region

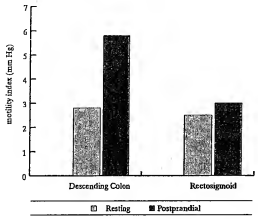


Table 2. Clinical presentation in patients with SCI due to UMN vs LMN injury

	UMN lesion	LMN lesion
Level of lesion	Above T10 vertebral or T12 spinal segment	Below T10 vertebral or T12 spinal segment
Transit time (Cecum to anus)	Increased	Increased
Motility of left colon	Decreased	Decreased
EAS	Spastic paralysis	Flaccid paralysis
Sympathetic output	Absent with lesions above T6 spinal segment	Retained
Symptoms	Constipation DWE Incontinence*	Constipation DWE Incontinence
Fecal impaction	Proximal colon	Rectal
Autonomic dysreflexia	Common with injuries above T6 level	Rare
Reflex defecation	Present	Not known

Constipation is <3 bowel movements per week; DWE or difficulty with evacuation is a combination of constipation with bloating, discomfort, pain, and prolonged bowel care sessions; * Patients with SCI due to UMN injury develop incontinence due to loss of sensations and development of lax sphincter later due to use of frequent laxatives and enemas

longed transit time of the left colon in subjects with paraplegia compared to able bodied (AB) individuals [15,16]. Our group has studied colonic motility in different segments of the left colon after SCI (4 subjects with paraplegia and 4 with quadriplegia). The results were compared to findings in 6 matched AB individuals [17]. Motility was evaluated for 1 h before breakfast and for 1 h during meals.

Baseline as well as meal stimulated colonic motility was reduced in SCI subjects compared to AB individuals (*Fig. 2,3*). Regional variations were noted in the SCI group with a post prandial response seen only in the descending colon and not in the rectosigmoid (*Fig. 4*).

We also studied the effect of SCI on colonic contractions in 14 male volunteers (8 with chronic SCI and 6 healthy controls) 1 h before sleep, during the entire period of sleep and 1h after sleep [18]. It was shown that HAPC are absent during sleep in both SCI and control groups. However, arousal from sleep failed to restore HAPC in subjects with SCI [18].

It appears that prolonged colonic transit time and absence of HAPC contributes to constipation and difficulty with evacuation (DWE) after SCI. As colonic motility depends on adequate colonic parasympathetic tone, these results, in part, were consistent with an absolute or relative loss of such autonomic tone.

Bowel problems with chronic SCI

Problems with defecation become more prominent as time progresses after the acute injury [1]. The clinical picture depends on whether the injury is upper motor neuron (UMN) (above vertebral T10 level) or lower motor neuron (LMN) (below vertebral T10 level) as shown in *Tab. 2*. Problems with defecation in both types of injuries have a significant impact on quality of life in individuals with chronic SCI given the prolonged amount of time spent on their bowel care [1,6-8,19].

In addition, complications such as fecal impaction and autonomic dysreflexia can occur. Fecal impaction is the most common problem often presenting with atypical symptoms such as paradoxical diarrhea, abdominal pain, nausea, vomiting, acute confusional states, urinary symptoms, and rectal bleeding due to pressure ulcerations [20]. Autonomic dysreflexia, occurs in patients with SCI above T6 spinal segment. It is due to an autonomic response to stimuli such as fecal impaction, bladder distension, catheterization, digital rectal stimulation, and colonoscopy [21,22]. Common symptoms are pounding headache, sweating, parasthesias, nasal obstruction, and goose flesh. Hypertension is the most common clinical sign and is seen in 90% of these cases [21]. Although rare, potentially fatal complications of autonomic dysreflexia include seizures and subarachnoid hemorrhage [23].

Management

Effective bowel management in individuals with SCI is of utmost importance. An adequate bowel regimen depends on many factors and will vary from patient to patient, but achieving effective evacuation and preventing incontinence is the common goal [24]. It is, therefore, important to completely evaluate the patient before designing a bowel regimen for any patient with a SCI.

Table 3. Conventional management strategies for bowel symptoms in SCI individuals

1.	Dietary changes
	a) Fiber diet
	b) High fluid intake
	c) Avoid foodstuffs which cause problems
2.	Positioning during bowel care
	a) Toilet seat/commode chairs
	b) Left lateral position for bowel care in bed
3.	Stimulation
	a) Digital stimulation of rectum
	b) Abdominal belt
4.	Fiber
	a) Soluble (pectin, guar, ispaghula, etc.)
	b) Insoluble (cellulose, lignin, etc.)
5.	Laxatives
	a) Bulk laxatives (docusate sodium, potassium)
	b) Stimulant laxatives (senna, bisacodyl, castor oil, etc.)
	c) Saline laxatives (magnesium hydroxide, sodium citrate, sodium biphosphate)
	d) Hyperosmolar laxatives (lactulose, sorbitol, polyethylene glycol)
6.	Suppositories
	a) Vegetable oil based bisacodyl suppository
	b) PEG based bisacodyl suppositor
	c) CO2 suppository
7.	Enemas
	a) Plain water enemas
	b) Fleet enema (sodium biphosphate)
	c) Therevac (TVC) mini enemas
8.	Prokinetic drugs
	a) Metoclopramide for short term use
	b) Cisapride not available for routine use
	c) Other agents like tegaserod require further evaluation
9.	Surgical options
	a) Sacral posterior rhizotomy
	b) Sacral anterior nerve root stimulation
	c) Appendicostomy and antegrade continent enema of Malone (MACE)
	d) Colostomy

History

There should be particular emphasis on duration and level of injury, bowel habits before the SCI and pre-SCI dietary habits (fluids, fiber, meal frequency, spices, amount). Medications with potential effects on bowel function should be ascertained and the social support system of the individual should be evaluated.

Physical examination

Patients with SCI may not report symptoms [1,6-8,19]. Particular emphasis should be placed on the person's nutritional and hydration status, the abdominal examination (distension, bowel sounds, tenderness, rigidity, fecal impaction, organomegaly), the rectal examination (hemorrhoids, sphincter tone, impaction, masses, stool guiac), and the neurological examination (level and nature of injury).

Laboratory evaluation

Laboratory evaluation should include a complete blood count, electrolytes, renal and liver function tests, amylase, and plain x-ray of abdomen.

Conventional measures for bowel care

Effective bowel care for individuals with SCI usually involves a number of different strategies (*Tab. 3*). Depending on the social needs and the bowel habits of the individual, frequency of bowel care can be tailored to each individual. Whenever possible, bowel care should be performed in either a normal position or the left lateral position [25]. Digital rectal stimulation (DRS) can also be useful [26]. In our own evaluation of 6 subjects with SCI (4 paraplegics and 2 with quadriplegia), use of DRS was shown to increase both the amplitude and frequency of colonic contractions of the left colon [27]. This anocolonic reflex probably involves stretch receptors in the IAS which increase the parasympathetic output to the left colon. All these patients had SCI of UMN type and whether a similar reflex is present in those with SCI of the LMN type is not known [27]. Diet has an important place in these individuals and minor changes in the diet can help these individuals tremendously. It is important for these individuals to consume adequate amounts of fiber and drink at least 2-3 liters of fluids every day [28]. Supplemental fiber may be needed if dietary intake is inadequate (<30 g/d). Fiber produces uniform stool consistency by absorbing excess water [29,30].

Laxatives are often employed as an adjunct to routine bowel care (*Tab. 3*). Bulk laxatives such as docusate and osmotic laxatives such as lactulose are the most commonly employed preparations [31,32]. Enemas are not promoted for routine use unless needed for fecal impaction.

These conventional strategies are time consuming and expensive and do not target the basic pathology of decreased colonic motility. Perhaps as a result, routine bowel care regimens do not yield satisfactory results in many patients. Hence, there is a need of more effective agents which attempt to reverse the basic pathophysiology after SCI.

Newer modalities

Cisapride, a prokinetic drug acts by increasing the release of acetylcholine from post-ganglionic nerve endings. Studies have documented a reduction in mouth-anus transit time and mouth to cecum transit time in subjects with quadriplegia using this drug [13,33]. We have shown the effect of cisapride in improving MCTT in subjects with SCI [13]. Though generally safe, cisapride has been linked to serious cardiac arrythmias (torsades de pointes) and has been withdrawn from the market [34].

Neostigmine, an inhibitor of enzyme acetylcholinesterase, results in increased levels of acetylcholine at the nerve endings and increases colonic peristalsis. It has been used successfully in patients with acute intestinal pseudo-obstruction [35]. Unfortunately, neostigmine also increases airway resistance and causes bradycardia in a significant number of patients. However, we have shown that these unwanted side effects can be prevented if neostigmine is administered together with glycopyrrolate. The latter is an anticholinergic which appears to spare the muscarinic receptors of the colon [17]. Recently, we have shown

Figure 5. Semi-quantitative measure (score of 0 to 4) of bowel emptying using barium oat-meal paste. Evacuation scores: a=1, b=2, c=3, and d=4

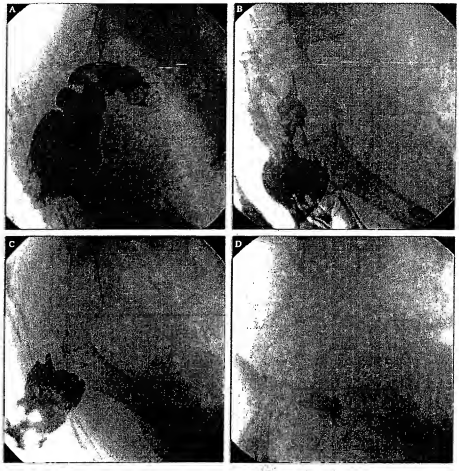


Figure 6. Histogram showing the effect of normal saline (control), IV neostigmine (2 mg), and IV neostigmine (2 mg) + glycopyrrolate (0.4 mg) on evacuation of oat-meal barium paste from the rectum and descending colon. The evacuation score was 3 or more in most subjects receiving neostigmine (57%) or combination of neostigmine and glycopyrrolate (64%). None of the subjects scored 2 or more after normal saline

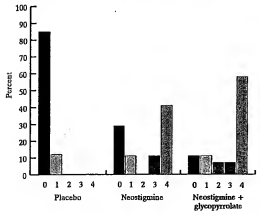
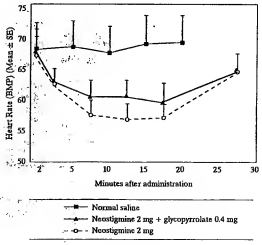


Figure 7. Comparison of the effect of normal saline, neostigmine, and neostigmine + glycopyrrolate on the mean heart rate at 5 min intervals



beneficial effects of neostigmine on the gastrointestinal tract in individuals with SCI [36]. Thirteen individuals with SCI (5 with quadriplegia and 8 with paraplegia) were infused normal saline, neostigmine 2 mg, or neostigmine 2 mg with glycopyrrolate 0.4 mg on separate days. Bowel evacuation was measured by videofluoroscopy after rectal instillation of 200 ml of oat-meal paste of barium (having the consistency of soft stool). Evacuation was measured by an X-ray taken after 30 min and compared with a baseline X-ray (*Fig. 5*). In addition, airway resistance and hemodynamic parameters (pulse and blood pressure) were assessed. Both neostigmine and the combination of neostigmine with glycopyrrolate resulted in better evacuation compared with normal saline (*Fig. 6*) [36].

Although both neostigmine alone and neostigmine with glycopyrrolate resulted in bradycardia, lowest heart rates were recorded when neostigmine was given alone (*Fig. 7*). Both total and central resistance increased with neostigmine relative to normal saline, whereas, neostigmine with glycopyrrolate reversed this (+27% and +17% vs –10% and –8% respectively). The drug was well tolerated except for mild and transient (<30 min) muscle twitching (92%) and abdominal cramps (in those with injury below T10). Although intravenous infusion is not practical for routine clinical use, it remains to be established whether other routes of administration such as subcutaneous or intramuscular are effective in management of these individuals. These trials are ongoing and appear to be encouraging [37].

Tegaserod, a 5HT-4 (serotonin) receptor agonist is another agent with a potential for managing bowel symptoms in SCI. Serotonin has been documented as one of the neurotransmitters implicated in colonic motility [12,38]. Tegaserod in experimental studies has demonstrated an increase in both small bowel and colonic transit [39,40]. The drug has been successfully used in individuals with IBS, pseudo-obstruction, and habitual constipation [41-43]. There are no available data of its use in SCI and this is an area which needs to be explored.

Beneficial effect on the colonic motility of another 5-HT4 agonist, mosapride has been shown in a guinea pig model of SCI (after destruction of L1-3 and S2-4 cords) [44]. In response to rectal distension with a rectal balloon instilled with water, rectal pressures (R-R reflex) and internal anal sphincter relaxation (R-IAS reflex) were recorded at baseline and after intravenous administration of mosapride. Reflex area was derived and expressed as positive values for rectal contractions and IAS relaxations. Reflex indexes (R-R and R-IAS) were calculated as relative ratio of the reflex areas at baseline (control) and after drug administration. The authors showed that mosapride, given intravenously, increased the R-R and R-IAS indexes in a dose dependent manner. These changes could be reversed by about 50% after intravenous administration of the 5-HT4 antagonist GR-113808 [44].

Colostomy is an option in patients with severe and intractable problems [45,46]. It is also frequently advocated as an adjunct in the treatment of perineal pressure ulcers. Stone, et al. [46] showed that objective testing of the transit time can help in deciding the site of colostomy. A sigmoid colostomy is an option for those with normal colonic transit time and inability to adequately evacuate rectum. In contrast, a right transverse colostomy is useful for those with prolonged left colonic transit time. An ileostomy is generally reserved for individuals with a dilated, non-functional right colon. Stone, et al. [46], using a questionnaire, showed that colostomy simplified bowel care, relieved abdominal distension, and prevented fecal incontinence. The time spent in bowel care also decreased significantly from 98.6 min/day before colostomy to 17.8 min/day after colostomy. These individuals represent a high risk for abdominal surgery and selection of the patient is, therefore, important. In a small series, Deshmukh, et al. [47] reported a 15% mortality after colostomy in individuals with large pressure ulcers.

Moreover, Stone, et al. [46] noted postoperative complications in 10% individuals who underwent this procedure. All 27 patients in the first report had a colostomy performed for pressure ulcers whereas in the later, 13 out of 20 patients had colostomy for chronic intractable GI problems (one for rectal cancer), only 7 of 20 had this procedure for pressure ulcers. The authors in the later study performed colonic transit time and anorectal manometry in 6 patients in order to select the colostomy site. These differences could possibly explain the difference in mortality in the two reports. On the whole, it is an acceptable procedure provided it is done in a properly selected person at an appropriate time [45-47].

Surgical posterior rhizotomy and sacral anterior root stimulation are other surgical options shown to have therapeutic utility in SCI patients [48,49]. However, the high overall costs of these procedures has limited their utility. Cutaneous appendicoecostomy has been used to treat intractable incontinence in these patients.

Initially used by Malone, the technique (Malone Antegrade Colonic Enema or MACE) involves administration of enemas through the opening when required [50].

The technique has been shown to be successful in 57% of SCI patients with significant improvement in their QOL [51]. Bowel cleansing can also be accomplished in retrograde fashion using 'pulsed irrigation evacuation' (PIE) [52].

However, its efficacy remains to be determined in a controlled clinical trial.

Management of GI complications

The presenting symptoms of acute abdomen in SCI are quite variable given the sensory loss that accompanies SCI. Therefore, non-specific symptoms such as abdominal distension, vomiting, constipation always require a thorough evaluation.

An accurate diagnosis requires a careful clinical examination, laboratory evaluation, and expedited imaging studies (plain abdominal X-ray and CT scan of the abdomen).

Autonomic dysreflexia (AD) Prevention is the first step in treatment. Once recognized, however, AD should be treated as a medical emergency. If possible the stimulus should be identified and immediately removed. If needed, nifedipine and topical nitrates can be used for emergency control of the blood pressure [21].

Fecal impaction Rectal examination should always be performed if fecal impaction is suspected. If the rectum is empty, imaging is required to assess for more proximal impaction or signs of obstruction. To avoid complications, impaction

should be addressed quickly; delaying treatment for more than 3 days can be hazardous [20]. When an impaction exists, manual evacuation is the first option and requires proper lubrication and local anesthesia. When the impaction is beyond the reach of finger, sigmoidoscopic lavage can be effective. In addition, gastrografin and golytely have been effective [53]. If these procedures fail, surgery is a last resort.

Colorectal cancer (CRC) screening

Individuals with SCI are at risk of acquiring the same degenerative conditions including cancer, as able bodied people. In a population based study in veterans, the incidence of CRC in patients with SCI similar to that in the general population [54].

The anatomic distribution of CRC was also the same as in the general population with two third of the lesions occurring on the left side or the rectum [54]. However, in contrast to able bodied population, 60% of these tumors were found to be quite advanced (stage III or IV) at the time of presentation. The inability to differentiate symptoms of colorectal carcinoma from other GI complaints in individuals with SCI probably accounts for the delay in diagnosis of colorectal cancer [54]. Even more than in able bodied individuals, early detection and cure of CRC requires regular colonoscopy as a routine measure.

Colonoscopy in individuals with SCI has unique features. Not only must the preparation of the colon be adapted to SCI, but the performance of the procedure must be modified. In this respect, we have found that a two day preparation with oral phosphosoda and golytely is often required. Moreover, we have noted that SCI patients have difficulty in retaining the insufflated air, have lower cecal intubation rate (82%) and have relatively poor colon preparation.

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REVIEW ARTICLE

Drugs Aging 2008; 25 (10): 807-821
1170-229X/08/0010-0807/$48.00/0

Management of Chronic Constipation in the Elderly

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Contents

Abstract

Constipation is a significant healthcare problem in the elderly. However, while undoubtedly common in the elderly, data on the prevalence of constipation in general and of its subtypes vary considerably, depending on the nature of the study population and their location. Furthermore, the complexity of the pathophysiology of constipation in this age group is little appreciated. Assumptions regarding 'age-related changes in colorectal physiology' are, for the most part, not supported by scientific evidence and may serve to distract the clinician from uncovering the contributions of co-morbid diseases and the impact of iatrogenic factors. The evidence base from which one can develop recommendations on the management of constipation in the elderly is, for the most part, slim. This becomes most starkly apparent when one attempts to critically assess specific approaches to manage-

ment. There is insufficient evidence to support the use of many commonly used laxatives both in the general population and in the elderly. Lifestyle interventions have value for some patients but data are lacking on the benefits of these interventions for patients with chronic constipation. Data in the elderly do not exist for most new pharmacological approaches to constipation. Pending the availability of good data, management of constipation in the elderly should be tailored to each individual's needs and expectations, regardless of age or place of residence. In certain situations, constipation may be complicated by the development of impaction; preventive strategies are important in this context. We urge enrolment of many more elderly individuals with chronic constipation in clinical trials designed to address their particular needs.

Chronic constipation is highly prevalent in the elderly, with up to 20% of the community-dwelling elderly and 50% of the institutionalized elderly reporting symptoms of the disorder.[1,2] The condition impacts negatively on quality of life[3,4] and adversely affects the healthcare system in terms of resource utilization and cost. Chronic constipation is one of the most common reasons for attendance at general practitioners and gastroenterologists[5,6] and laxatives are amongst the most frequently prescribed medicines.[7] However, there is a paucity of good quality evidence on which to base management decisions, particularly in the elderly. This article reviews the available management options for this common, but often refractory, condition in the elderly.

For this review, we performed an electronic search of the PubMed and Cochrane databases for articles published before 2007 and a manual search through major journals for articles located through PubMed. Search terms were 'faecal impaction', 'anismus', 'pelvic floor dysfunction', 'constipation', 'pathophysiology', 'treatment', 'laxatives', 'randomized controlled trial', 'review' and 'elderly'. Further articles were retrieved based on literature cited in papers found using the initial search strategy.

1. Definition of Constipation

Constipation can be defined in many ways ranging from a simple quantitative assessment of bowel movement frequency to explicit diagnostic criteria. Surveys in the Western world show that more than 90% of people have between three bowel movements per day and three per week.[8-11] Consequently, many clinicians define constipation as a reduction in bowel movement frequency to fewer than three bowel movements per week.[2,12] However, there may be difficulties with such a quantitative definition of constipation, as many people tend to underestimate their stool frequency[13] and patients' perceptions of constipation do not always relate to stool frequency. Patients chiefly identify constipation on the basis of qualitative symptoms such as prolonged time to stool, difficult passage of stool, hard/lumpy stools, need for manual manoeuvres to pass stool, feeling of incomplete evacuation and abdominal bloating.[2,12]

Diagnostic criteria have been developed in an attempt to standardize the definition of chronic functional constipation. Among the most widely used are the so-called Rome criteria which, though evidence based, rely for their final definition on the consensus of an international committee (table I).[14,15] While a standardized definition is useful for clinical research, expert opinion suggests that widespread use of these criteria is restrictive and impractical. Observational studies indicate that many patients who report 'constipation' do not fulfil the Rome criteria for chronic functional constipation.[2,16] The American College of Gastroenterology (ACG) Chronic Constipation Task Force and the American Gastroenterological Association therefore recommend adoption of broader definitions of chronic constipation that can be used in everyday clinical practice.[12,17] These incorporate the symptoms most commonly expressed by patients who report constipation for ≥3 months (table I).

Table I. Definitions of chronic constipation

Rome III criteria for functional constipation[15]
Presence of two or more of the following:
straining during ≥25% of defecations
lumpy or hard stools in ≥25% of defecations
sensation of incomplete evacuation for ≥25% of defecations
sensation of anorectal obstruction/blockage for ≥25% of defecations
manual manoeuvres to facilitate ≥25% of defecations (digital manipulations, pelvic floor support)
fewer than three evacuations per week
loose stools are rarely present without the use of laxatives
Insufficient criteria for irritable bowel syndrome
Criteria fulfilled for the last 3 months, and symptom onset ≥6 months prior to diagnosis
American College of Gastroenterology definition of chronic functional constipation[17,18]
Symptom-based disorder defined as unsatisfactory defecation and characterized by infrequent bowel movements, difficult stool passage or both. Difficult stool passage includes straining, sense of difficulty passing stool, incomplete evacuation, hard/lumpy stool, prolonged time to defecation or passage of stool or need for manual manoeuvres to pass stool. Chronic constipation is defined as the presence of these symptoms for ≥3 months
American Gastroenterological Association definition of constipation[16]
Symptom-based disorder defined as unsatisfactory defecation and characterized by infrequent bowel movement, difficult stool passage or both. Difficult stool passage includes straining, sense of incomplete evacuation, hard/lumpy stool, prolonged time to defecate or pass stool or need for manual manoeuvres to pass stool

2. Prevalence of Constipation

In a systematic review of the epidemiology of constipation in North America, Higgins and Johanson[19] reported a prevalence range of 1.9–27.2%, with most estimates ranging from 12% to 19%. This wide range of prevalence estimates probably reflects differences in diagnostic criteria, as well as study population and methodology. Several studies report a higher prevalence of constipation in older age groups.[5,19-23] However, other studies describe similar[2] or even lower rates of constipation[1] in the elderly compared with the general population.

Among the community-dwelling elderly, the prevalence of chronic constipation is reported to be about 15–20%, with women having two to three times higher rates of constipation than men.[1,2,21,22,24,25] In nursing home residents, there is even larger variation amongst estimates of constipation prevalence. Many studies report that up to 50% of nursing home residents experience constipation and 50–74% of residents use laxatives on a daily basis.[13,26,27] However, Robson et al.[28] reported a much lower point-prevalence rate of 12.5% and a 3-month incidence of 7% in a large survey of 21 000 nursing home residents. This relatively low prevalence rate might be explained by the limited diagnostic criteria used in this study.

Despite the lack of rigorously designed prevalence studies, there can be no doubt that constipation is a significant health problem in the elderly. The disorder impacts negatively on an elderly individual's quality of life[3,4] and adversely affects the economy in terms of physician and laxative-prescription costs. Over 13 million general practitioner prescriptions were written for laxatives in England in 2006,[7] and the elderly likely account for a substantial portion of these.

3. Pathophysiology of Constipation in the Elderly

3.1 Age-Related Changes in Bowel Structure and Function

Constipation is associated with increasing age.[5,19-23] However, the condition is not a physiological consequence of normal aging. Indeed, most healthy, active elderly individuals have normal bowel function.[20] Age-related alterations in ano-rectal physiology have been described, but these are rarely the sole cause of constipation in the elderly. Such changes include decreased rectal compliance and diminished rectal sensation, which may result in larger rectal volumes being required to elicit the urge to defecate. Age is also associated with a significant reduction in anal canal squeeze pressure in women[29-32] but not in men, a differential change that does not appear to be explained by parity. Resting anal pressures are lower in both genders,[29,33] and such changes in sphincter pressure may predispose the elderly to faecal incontinence. Changes in colonic motility have not been consistently demonstrated in the elderly. Although one study indicated significant prolongation of colonic transit time with advancing age,[34] other studies showed no significant change.[35,36] Similarly, stud-

ies of colonic motor or myoelectric activity have not revealed significant age-related changes.[37]

3.2 Primary or Idiopathic Constipation

3.2.1 Normal Transit Constipation

Normal transit constipation is the most frequent type of constipation. Patients often complain of abdominal pain and bloating, difficult passage of stools or hard stools.[38] However, transit time and stool frequency are within normal range. Many would regard this disorder as a component of the irritable bowel syndrome.

3.2.2 Slow Transit Constipation

Slow transit constipation is characterized by prolonged intestinal transit time and has been attributed to various pathophysiological mechanisms. These include colonic dysmotility as a result of altered nitric oxide production,[39] diminished gastrocolic reflex activity,[40] altered regulation of the enteric nervous system[41] and altered concentrations of intestinal neuropeptides such as substance P and vasoactive intestinal polypeptide.[42]

3.2.3 Outlet Constipation (Dyscoordinated Pelvic Muscle Activity/Pelvic Floor Dyssynergia)

Normal defecation involves coordinated relaxation of the external anal sphincter and puborectalis muscles, increased intra-abdominal pressure and inhibition of colonic segmenting activity. In patients with defecatory disorders, there is a paradoxical contraction of the external anal sphincter and puborectalis muscles during the defecatory process and alterations in the anorectal inhibitory reflex.[5,43] Feelings of incomplete evacuation and straining are key features. Anal fissures, haemorrhoids, rectal prolapse, posterior rectal herniation and rectocoele may all contribute to disordered defecation.[44]

3.3 Secondary Constipation

Many age-related problems contribute to the increased prevalence of constipation in the elderly (table II).

4. Complications of Constipation

The major consequences of constipation include faecal impaction and incontinence. Faecal impaction may lead to urinary retention and increase the risk of urinary tract infections. Its occurrence is especially likely among those with cognitive or sensory impairment, such as the nursing home patient with

Table II. Medical disorders and medications associated with constipation in the elderly

Gastrointestinal disorders
Colorectal tumour
External compression (e.g. from a tumour)
Diverticular disease
Strictures (inflammatory, post-diverticulitis, post-ischaemic, post-radiotherapy)
Rectal prolapse
Rectocoele
Volvulus
Megacolon
Irritable bowel syndrome
Haemorrhoids
Anal fissure
Neurological disorders
Autonomic neuropathy
Parkinson's disease
Cerebrovascular disease
Depression
Dementia
Spinal cord lesion
Multiple sclerosis
Myopathic disorders
Amyloidosis
Dermatomyositis
Systemic sclerosis
Endocrine and metabolic disorders
Diabetes mellitus
Hypothyroidism
Hyperparathyroidism
Multiple endocrine neoplasia II
Hypercalcaemia
Hypokalaemia
Hypermagnesaemia
Chronic kidney disease
Dehydration
Cardiac disorders
Congestive cardiac failure
Medications
Analgesics (opioids, NSAIDs)
Antacids (aluminium or calcium containing)
Anticholinergics (tricyclic antidepressants, antihistamines, antipsycholics, antispasmodics)
Antiepileptics
Antidepressants (tricyclic antidepressants, monoamine oxidase inhibitors)
Anti-parkinsonian drugs
Calcium channel antagonists
Calcium supplements
Diuretics (furosemide, hydrochlorothiazide)
Iron supplements

Alzheimer's disease. Faecal impaction may also lead to intestinal obstruction or even colonic (stercoral) ulceration, in severe cases. Excessive straining at stool can affect cerebral, coronary and peripheral arterial circulation with the resultant possibility of syncope or cardiac ischaemia. Excessive straining also contributes to haemorrhoids, fissures and rectal prolapse.

5. Assessment of the Elderly Individual with Constipation

A detailed discussion of the investigation of the constipated patient is beyond the scope of this article. Suffice it to say that given the likelihood of both co-morbidity and polypharmacy (table II) in this population, very careful attention should be directed to the identification of primary disease processes and iatrogenic causes of constipation. The search for intrinsic lesions of the colon should be directed by the clinical scenario; as in other age groups, the yield from invasive tests, such as colonoscopy, in otherwise uncomplicated and long-standing constipation is likely to be very low.[18] In deciding on whether or not to embark on such tests, the clinician should be guided by the nature and duration of the history and the presence or absence of symptoms suggestive of other organic disease. Plain abdominal radiographs are of value in defining faecal loading and megacolon and may provide the first hints of obstruction. More specialized tests of colorectal or pelvic floor function are of limited value because of the relative paucity of specific interventions.

6. Management of Chronic Constipation in the Elderly

6.1 Aims

The aims of treatment of chronic constipation are to relieve symptoms, restore normal bowel habit, i.e. the passage of a soft, formed stool at least three times a week without straining, and to improve quality of life with minimal adverse effects. Treatment should be individualized for each patient according to identified causes.

6.2 General Measures (Non-Pharmacological Treatment)

Any elderly individual presenting with constipation should have a thorough review of their medications. Medications that can cause constipation should be replaced with an appropriate alternative medicine, where possible. It is often suggested that diet, hydration and physical activity be addressed in the elderly individual with constipation. However, a true causal link between these factors and constipation has yet to be established and there are no randomized controlled trials that have tested these interventions. Most evidence comes from observational studies.

Dehydration is frequently acknowledged as a risk factor for constipation and has been associated with slowed transit times in some observational studies.[45] However, there are no randomized controlled trials or systematic reviews of advice to increase fluid in adults with chronic constipation. Caution should be exercised when replacing fluids in the elderly with renal or cardiac failure.

Foods with a high residual fibre content (e.g. bran and other whole grains, nuts, vegetables) are often recommended for the management of constipation. However, a diet poor in fibre should not always be assumed to be the cause of chronic constipation.[46] The best way to add fibre is by making subtle changes to the diet. The changes should be made gradually to avoid abdominal pain and bloating, which can occur with ingestion of fibre. Some patients may be helped by a fibre-rich diet, but many patients with more severe constipation have worse symptoms, for example, bloating and excessive gas, when increasing dietary fibre intake, thus limiting the applicability of this recommendation. In patients with idiopathic megacolon or other causes of colonic dilatation (e.g. bowel obstruction or megarectum), fibre supplementation should be avoided. These patients require a fibre-restricted diet with a regular schedule of laxatives or enemas to minimize faecal retention and impaction.[47] Faecal impaction should be removed before initiation of fibre therapy. Foods containing complex carbohydrates, such as prunes or melons, can also help normalize bowel movements.

Table III. Graded recommendations and levels of evidence for treatments of chronic constipation

Grade	Support	Evidence	Agents
American College of Gastroenterology Chronic Constipation Task Force[17,18]			
A	≥2 level 1 trials without conflicting evidence from other level 1 trials	Level 1: RCTs with $p < 0.05$; adequate sample size; appropriate methods (high quality)	Polyethylene glycol (PEG 3350), lactulose, tegaserod
B	Single level 1 trial or ≥2 level 2 trials with conflicting evidence from other level 1 trials or ≥2 level 2 trials	Level 2: RCTs with $p > 0.05$; or inadequate sample size; and/or inappropriate methods (intermediate quality)	Psyllium (ispaghula), polycarbophil, methylcellulose, bran, stool softeners, milk of magnesia (magnesium hydroxide), stimulant laxatives
C	Level 3–5 trials	Level 3: non-RCTs with contemporaneous controls	Herbal supplements, alternative treatments, lubricants, combination laxatives
		Level 4: non-RCTs with historical controls	
		Level 5: case series	
Ramkumar and Rao[53] systematic review			
A		Good evidence (level 1): consistent results from well designed, well conducted studies	Polyethylene glycol, tegaserod
B		Fair evidence (level 2): results show benefit, but strength is limited by the number, quality or consistency of the individual studies (fair quality)	Psyllium, lactulose
C		Poor evidence (level 3): insufficient because of limited number or power of studies or flaws in design or conduct (poor quality)	Magnesium hydroxide, polycarbophil, methylcellulose, senna, bisacodyl, docusate preparations, bran, colchicine, misoprostol

RCTs = randomized controlled trials.

Data concerning the relationship between physical activity and constipation in the elderly are also limited. Some observational studies suggest a protective effect,[23] whereas data from interventional trials are conflicting.[48] However, low-to-moderate levels of exercise are associated with a range of health benefits for people of all ages. One cohort study of 39 532 women in Australia found that women who were more physically active were less likely to report having constipation "sometimes or often" than women who were less physically active (comparison of most active group vs least active group by age group; odds ratio [OR] for constipation: 0.58, 95% CI 0.47, 0.73 in women aged 18–23 years; 0.72, 95% CI 0.63, 0.83 in women aged 45–50 years; and 0.72, 95% CI 0.61, 0.85 in women aged 70–75 years).[49]

The importance of establishing a routine that promotes normal bowel function should be emphasized. This includes taking advantage of the gastrocolic reflex, which, for most individuals, is most pronounced after breakfast or supper. The need to respond as soon as possible to any urge to defecate should also be emphasized.

6.3 Pharmacological Treatment

Laxatives are amongst the most commonly prescribed medicines in the US and the UK.[7,50] However, the evidence base supporting their use, especially in the elderly, is often poor.[51] There have been a number of systematic reviews of various treatments for chronic constipation in recent years.[17,18,52,53] In 2005, the ACG Chronic Constipation Task Force published recommendations on the management of chronic constipation in North America.[17,18] In addition, Ramkumar and Rao,[53] also in 2005, published a systematic review of the efficacy and safety of traditional medical therapies for chronic constipation. These systematic reviews included all randomized controlled trials evaluating treatments for constipation, but were not limited specifically to trials among the elderly. Table III outlines the levels of evidence and grading recommendations for the various agents that were analysed in these systematic reviews. Laxatives can be classified into bulk laxatives, osmotic laxatives, stimulant laxatives and stool softeners. Some newer agents such as lubiprostone and tegaserod are also discussed in the following sections, in addition to

the evidence pertaining to use of laxatives in the elderly.

6.3.1 Fibre and Bulk-Forming Laxatives

The principal fibre and bulk-forming laxatives are psyllium (ispaghula), bran, methylcellulose and polycarbophil. These agents increase the weight and water-absorbent properties of the stool, thereby increasing faecal bulk and accelerating luminal propulsion. Increased gastrointestinal motility results in more rapid colonic transit time and increased frequency of bowel movements.[52,54] Fibre and bulk-forming laxatives may take several days to have an effect and patients taking them are usually advised to drink plenty of fluid so as to avoid mechanical obstruction. However, the necessity and effectiveness of additional fluid remain unproven. Common adverse effects of bulk-forming laxatives include bloating, flatulence and abdominal pain. Such effects are frequently reported with natural fibre (psyllium) and are attributed to bacterial degradation. Adverse effects are less problematic with methylcellulose, a semisynthetic fibre, and non-existent with polycarbophil, a synthetic polymer of acrylic acid.

Psyllium (Ispaghula)

Psyllium is a derivative of the husk of *Plantago ovata*. Both systematic reviews of treatments for chronic constipation[17,18,53] gave psyllium a grade B recommendation, i.e. moderate evidence to support its use in the treatment of constipation. Compared with placebo, psyllium appears to increase stool frequency.[55] However, there are conflicting data concerning gut transit times, with one study suggesting that total gut transit time improves[56] and another suggesting that there is no change in gut transit.[57] The effect of psyllium on stool consistency in these trials was also conflicting, with Ashraf et al.[56] suggesting no change but Cheskin et al.[57] suggesting significant improvement. Some studies of psyllium have been conducted specifically in the elderly. A small randomized, single-blind trial in seven patients with Parkinson's disease (mean age 66 years, range 54–80 years) showed that psyllium treatment was associated with increased stool frequency over a 16-week follow-up period.[58] In elderly nursing home patients, psyllium and polycarbophil calcium have been noted to be similar in their effect in improving stool frequency, stool consistency and ease of defecation.[59] In an open-label trial conducted in a general population, Dettmar and Skyes[60] compared psyllium with other laxatives. Psyllium was noted to be superior to three different stimulant/irritant laxatives, as well as lactulose and magnesium sulfate, in the treatment of constipation and was more palatable and acceptable to patients. A study of psyllium versus docusate sodium (sodium dioctyl sulfosuccinate) found that psyllium was superior to docusate sodium in its effect on stool frequency, stool water content, total stool output and a combination of several objective measures of constipation.[61] However, the mean age of the patients in this study was 37.2 years and adverse events were not documented in the trial.

Bran

Bran received a grade C recommendation from Ramkumar and Rao[53] and a grade B recommendation from the ACG Chronic Constipation Task Force.[17,18] Some studies of bran have specifically been performed in populations of elderly individuals. In a study of patients aged >60 years living in an extended care facility, the effect on constipation of 0.5–1.5 g of bran was compared with that of a regular diet.[62] There was a decrease in laxative requirements in patients taking bran, but these patients also seemed to require more assistance with actual defecation in terms of increased use of enemas and suppositories. A smaller study compared wheat bran 1.5–4.5 g with a regular diet in elderly long-stay geriatric patients with a mean age of 80 years and showed significant improvement in stool frequency and consistency and no significant difference in laxative or suppository requirements.[63] Another trial investigated the relationship between clinical response to dietary fibre treatment and transit in a sample of 149 patients (mean age 53 years, range 18–81 years) with chronic constipation.[64] Eighty-five percent of patients with normal transit constipation improved or became symptom-free. Eighty percent of patients with slow transit and 63% of patients with a disorder of defecation did not respond to dietary fibre treatment. Tramonte et al.[52] conducted a systematic review and found no differences between bulk laxatives and other laxatives in bowel movement frequency.

Methylcellulose

Methylcellulose received a grade C recommendation from Ramkumar and Rao[53] and a grade B recommendation from the ACG Chronic Constipation Task Force.[17,18] One study compared 1, 2 or 4 g of methylcellulose or 3.4 g of psyllium in 50 healthy patients with the same treatment in 59 chronically constipated patients; the mean ages of the two groups were 27 (range 18–70) and 28 (range 18–70) years, respectively.[65] In both healthy and constipated patients, there was a statistically significant increase in bowel movement frequency and no difference in the incidence of abdominal cramps, flatulence or abdominal pain between the treatment and placebo periods. However, the lack of an appropriate control group hampers interpretation of the results of this study.

6.3.2 Osmotic Laxatives

Osmotic laxatives are hyperosmolar agents that cause secretion of water into the intestinal lumen by osmotic activity, thus leading to a softer stool and improved propulsion. They include saline laxatives (magnesium sulfate, magnesium citrate, magnesium hydroxide and magnesium phosphate), poorly absorbed sugars (sorbitol and lactulose), macrogols (polyethylene glycol [PEG 3350]) and glycerin (glycerol) suppositories. The individual compounds differ in their adverse effect profile (primarily flatulence) and effectiveness, principally because of differences in their digestibility by colonic bacteria. The onset of action of osmotic laxatives ranges from 0.5 to 48 hours;[38,66] saline laxatives can work within 0.5–3 hours, whereas poorly absorbed sugars and polyethylene glycol work within 24–48 hours. Electrolyte abnormalities (hypermagnesaemia, hyperphosphataemia, hypercalcaemia, hyponatraemia, hypokalaemia), hypovolaemia and diarrhoea have been reported with use of osmotic laxatives, but the precise incidence of these adverse events is unclear.[67] High doses of polyethylene glycol may produce diarrhoea, nausea, abdominal bloating, cramping and flatulence.[17,18]

Magnesium Salts (Saline Laxatives)

Magnesium salts received a grade C recommendation from Ramkumar and Rao[53] and a grade B recommendation from the ACG Chronic Constipation Task Force.[17,18]

Only one trial has assessed the effectiveness of milk of magnesia (magnesium hydroxide) for patients with chronic constipation and its conclusions are difficult to interpret because of the inclusion of multiple crossover periods.[68] The ACG Chronic Constipation Task Force felt that it was not possible to make any recommendation about magnesium hydroxide as a treatment for constipation, given the poor quality of this study design. Furthermore, use of magnesium in the elderly is limited by adverse effects such as flatulence, abdominal cramps and magnesium toxicity.[69] Magnesium also interferes with the absorption of several medications, including tetracyclines, digoxin, chlorpromazine and isoniazid. Hypermagnesaemia is more likely to be a problem in patients with renal failure. Hypermagnesaemia may also cause paralytic ileus which, in itself, can cause constipation. There are no trials that have evaluated use of magnesium sulfate (Epsom salts) in the treatment of constipation after 1966.

Lactulose

Lactulose received a grade B recommendation from Ramkumar and Rao[53] and a grade A recommendation from the ACG Chronic Constipation Task Force.[17,18] Lactulose is a non-absorbable synthetic dissacharide that is metabolized by colonic bacteria into lactic acid and other inorganic acids, which are in turn absorbed by the intestinal mucosa. The osmotic effect of lactulose usually occurs after 48–72 hours and results in increased colonic peristalsis. The main adverse effects of lactulose are bloating, flatulence and hypokalaemia.[70]

Three studies have compared lactulose with placebo: one included patients with a mean age of 28 years,[71] another with a mean age of >60 years[72] and, yet another, was among nursing home residents with a mean age of 84.7 years.[73] In the latter study, lactulose was superior to placebo with an increase in stool frequency, a reduction in the severity of cramping, flatulence and tenesmus, and a reduction in the number of faecal impactions.[73] Lactulose-treated patients needed fewer enemas than control patients and no adverse clinical or laboratory effects were noted. However, the numbers in these trials were relatively small at 24,[71] 103[72] and 47.[73] Compared with polyethylene glycol solution, lactulose is less efficacious and has more adverse ef-

fects.[74] An open-label, parallel study that compared lactulose, ispaghula and placebo suggested that the two treatment agents were equally effective in the treatment of constipation.[75]

Sorbitol

Sorbitol is a non-absorbable sugar alcohol that exerts its osmotic effect at the level of the colon. Lederle et al.[70] compared sorbitol with lactulose in a small sample of 30 elderly men aged 65–86 years and reported equal effectiveness. However, sorbitol is less expensive than lactulose and seems to produce less nausea. Abdominal pain and flatulence were equally frequent with both agents. These adverse effects may limit tolerability.

Macrogols

Polyethylene glycol received a grade A recommendation from both Ramkumar and Rao[53] and the ACG Chronic Constipation Task Force.[17,18] Polyethylene glycol is an iso-osmotic laxative that binds water molecules. It is not absorbed and not metabolized by colonic bacteria. Different preparations exist with molecular weights ranging from 3000 to 4000 kDa, but electrolyte loss is unlikely when polyethylene glycol is used in small volumes (10–30 g) as a laxative.[76] The volume of stools is increased and their consistency is softer, resulting in increased peristalsis. Many studies have demonstrated the efficacy of polyethylene glycol; however, very few have specifically included elderly patients.

In their review, Ramkumar and Rao[53] identified eight randomized controlled trials of polyethylene glycol. Five compared polyethylene glycol with placebo,[76-80] one compared polyethylene glycol with lactulose in patients with chronic constipation[74] and another evaluated the efficacy and tolerability of polyethylene glycol solutions, lactulose and placebo in relieving opioid-induced constipation.[81] The final study compared two doses of polyethylene glycol solutions: an iso-osmotic preparation and a hypo-osmotic preparation.[82] However, constipation was variously defined, with only two studies utilizing the Rome criteria to identify suitable patients. Only three of these trials included a proportion of patients aged >65 years.[76,77,82]

Adverse effects of polyethylene glycol include nausea, vomiting, diarrhoea, flatulence and abdominal cramps. In addition, fulminant pulmonary oedema has been reported with use of polyethylene glycol.[83,84] The precise mechanism is unclear, but it is thought that the osmotic properties of polyethylene glycol can induce pulmonary oedema when the agent is aspirated into the lungs. Use of polyethylene glycol with electrolyte solutions must be carefully managed in patients at high risk of aspiration, such as elderly patients with Parkinson's disease or supranuclear palsy.

6.3.3 Stimulant Laxatives

Stimulant laxatives received a grade C recommendation from Ramkumar and Rao[53] and a grade B recommendation from the ACG Chronic Constipation Task Force.[17,18] Both systematic reviews found insufficient data to make a recommendation about the effectiveness of stimulant laxatives in patients with chronic constipation.

Stimulant laxatives include anthroquinones (senna, aloe, cascara), diphenylmethane derivatives (bisacodyl, sodium picosulfate), castor oil (obselete due to risk of malabsorption, dehydration and lipoid pneumonia) and phenolphthalein (now withdrawn as shown to be carcinogenic). Stimulant laxatives increase intestinal motility and secretions by stimulating the colonic myenteric plexus and altering fluid and electrolyte transport. Their laxative effect is dose dependent since these agents inhibit the absorption of sodium and water at low doses and stimulate sodium and water influx into the colonic lumen at high doses.[38,85] The onset of action of stimulant laxatives usually occurs within 8–12 hours of administration but frail elderly patients may have a slower response. Stimulant laxatives can cause abdominal discomfort, electrolyte imbalance, allergic reactions and hepatotoxicity.[67] They have a less favourable adverse effect profile than other laxatives. Cathartic colon (a syndrome characterized by colonic dilatation and loss of haustration) has been reported in patients taking stimulant laxatives.[86] Whether or not stimulant laxatives cause permanent structural damage to the colon is unclear.[67,87] Senna-containing compounds have been associated with melanosis coli, though there is no clear association between melanosis coli and colorectal cancer.[67,88]

6.3.4 Stool Softeners

Stool softeners received a grade C recommendation from Ramkumar and Rao[53] and a grade B

recommendation from the ACG Chronic Constipation Task Force.[17,18] Evidence for their effectiveness is limited and they are no longer recommended for the treatment of constipation. Stool softeners include docusate sodium and docusate calcium. Docusate is of questionable efficacy,[89] has been associated with the development of faecal soiling in the elderly and is, therefore, not recommended for use in this age group. Liquid paraffin is no longer recommended as it may reduce absorption of fat-soluble vitamins and cause lipoid pneumonia if aspirated.

6.3.5 Prokinetic Agents

Prokinetic agents have traditionally been used for the treatment of upper gastrointestinal tract functional disorders, including gastro-oesophageal reflux disease, gastroparesis and dyspepsia. However, recently their effects on the lower gastrointestinal tract and their therapeutic potential in the treatment of constipation have been evaluated.[90-98] Of the prokinetic agents, cisapride is no longer available because of serious cardiac adverse effects and the risk of drug interactions with cytochrome P450 3A4 inhibitors. The motility-enhancing effects of many of the newer classes of prokinetics are mediated by stimulation of intrinsic cholinergic nerves in the gastrointestinal tract via activation of serotonin 5-HT$_4$ receptors.

Tegaserod

The prokinetic agent tegaserod received a grade A recommendation from both Ramkumar and Rao[53] and the ACG Chronic Constipation Task Force.[17,18]

Tegaserod is a presynaptic 5-HT$_4$ receptor agonist. It modulates fluid content through cyclic adenosine monophosphate-mediated release of chloride from colonocytes. Tegaserod stimulates the peristaltic reflex, increases colonic motility and decreases visceral hypersensitivity.[90-92] Several large, randomized, double-blind, parallel-group trials have evaluated the effectiveness of tegaserod (2 or 6 mg twice daily) in patients with constipation attributed to irritable bowel syndrome.[93-95] However, none of these trials specifically targeted elderly patients and all enrolled a majority of women (about 85%). Tegaserod has not been shown to be efficacious in male patients. Nevertheless, all studies showed that tegaserod is well tolerated and improves frequency of complete spontaneous bowel movements, straining, stool frequency and consistency in patients with chronic constipation. The main adverse effect reported in clinical trials was diarrhoea, though this was generally mild and transient, did not result in electrolyte imbalance and resolved with continued treatment. In these studies, the overall incidence of adverse effects with tegaserod was similar to that of placebo.[96] No clinically relevant drug interactions have been described with tegaserod and no dosage adjustment is required in elderly patients or in those with mild-to-moderate hepatic or renal impairment.[99] However, in the US, tegaserod has not been approved for use in patients aged >65 years; rather, it has been approved by the US FDA only for use in patients aged <65 years with chronic idiopathic constipation and for women who have irritable bowel syndrome with constipation. Furthermore, the sale and marketing of tegaserod in the US and elsewhere were suspended in March 2007 following the identification of an increased risk of cardiovascular events among patients who had received this drug. More recently, tegaserod has been re-introduced in a restricted manner for qualifying patients in the US. Tegaserod has not been approved for use in the EU.

Prucalopride

Prucalopride is a 5-HT$_4$ receptor agonist with prokinetic effects similar to tegaserod.[97] Two randomized, double-blind, placebo-controlled trials in patients with severe constipation (mean age 46 years) reported prucalopride to be more effective than placebo.[98,100] However, high-quality data supporting its use in the elderly are unavailable.

Erythromycin

Erythromycin is a potent stimulator of gastrointestinal motility as a result of its action as a motilin receptor agonist. However, the known distribution of motilin receptors throughout the gut does not suggest that erythromycin would have a significant effect on colonic motility. Nevertheless, Sharma et al.[101] undertook a pilot study to evaluate the effect of erythromycin on constipation in adults. In this open-label non-randomized trial, 11 male patients were treated for 1 month with erythromycin (1 g/day for 2 weeks, then 500 mg/day for 2 weeks). Both colon transit time and stool frequency im-

proved. Two patients complained of increased bowel sounds, but otherwise there were no significant adverse effects. Further studies of erythromycin for the treatment of constipation have not been reported. Use of erythromycin is also limited by its poor bioavailability when given orally and the risks of antibacterial administration.

Other non-antibacterial macrolides have been developed but none has been approved for constipation or any other condition to date.

6.3.6 Other Agents

Loxiglumide

Loxiglumide is a cholecystokinin receptor antagonist. It has been evaluated in a small prospective randomized, double-blind, controlled trial of 21 nursing home patients (mean age 83 years) with chronic constipation.[102] Thirteen male and eight female patients were randomized to receive either loxiglumide 800 mg three times daily or placebo. There was a statistically significant improvement in stool frequency from 3.9 per week in the placebo group to 4.8 per week in the treatment group. No serious adverse events were encountered.

Nizatidine

Nizatidine, a histamine H_2 receptor antagonist, has been reported to enhance colonic peristalsis in healthy young adults.[103] However, further research is warranted to define the role of this agent in the management of constipation.

Colchicine

Colchicine is usually used for the treatment of acute gout and familial Mediterranean fever. However, diarrhoea is a common and limiting adverse effect of this medication, a characteristic which has led to exploration of its potential as a treatment for constipation. Colchicine received a grade C recommendation from Ramkumar and Rao,[53] who concluded that there was insufficient evidence to support its use in the treatment of chronic constipation.

Colchicine has been evaluated in a randomized, double-blind, placebo-controlled trial of 16 chronically constipated patients (mean age 47 years, range 25–89 years, two patients aged >65 years).[104] In this study, colchicine was given at a dose of 0.6 mg three times daily over a 4-week period. This regimen significantly increased bowel movement frequency and decreased colonic transit time compared with both baseline values and placebo. No patient had serious adverse effects, but abdominal pain was reported more frequently with colchicine. There may also be a role for colchicine in the management of patients with Parkinson's disease and constipation[105] and in those with chronic constipation following colectomy with ileorectostomy for colonic inertia.[106]

Misoprostol

Misoprostol received a grade C recommendation from Ramkumar and Rao.[53] This drug is a synthetic prostaglandin E1 analogue that is used in the prevention and treatment of NSAID-induced peptic ulcer disease. Diarrhoea is a common adverse effect of misoprostol. Only one randomized trial has evaluated misoprostol in the management of chronic constipation.[107] This trial enrolled eight patients aged >18 years. Misoprostol significantly increased colonic transit time and stool frequency compared with placebo, but because of its small sample size the results of this study may not be generalizable.

Lubiprostone

Lubiprostone is a type 2 chloride channel activator that increases fluid secretion from the colon and, thereby, enhances stool passage. Based on data from randomized trials involving adults,[108] lubiprostone has been approved for the treatment of chronic constipation in adults in the US; specific data on the elderly are not available. The adverse effect profile of lubiprostone appears to be favourable.

Herbal Supplements, Alternative Treatments, Lubricants, Combination Laxatives

There are no published randomized controlled trials in the English literature of the efficacy of herbal supplements, lubricants or combination laxatives in the management of adult patients with chronic constipation.

6.4 Biofeedback and Sacral Nerve Stimulation

Patients using biofeedback techniques to control constipation are trained to relax their pelvic floor muscles during straining and to correlate relaxation and pushing to achieve defecation. In one uncontrolled study, biofeedback provided long-term benefit for patients with intractable, slow and normal

transit constipation.[109] This study followed 100 patients over a 23-month period. Straining, need for digital manipulation, pain and bloating were all significantly reduced immediately after biofeedback and after 23 months' follow-up. More recently, two randomized controlled studies have provided convincing evidence of efficacy for biofeedback in patients with pelvic floor dyssynergia.[110,111] There may be limitations to the application of this approach in some elderly individuals because of an inability to cooperate fully with the biofeedback programme.

Sacral nerve stimulation is now widely used in the management of faecal incontinence, and some preliminary data suggest a possible role for this approach in intractable constipation.[112]

6.5 Enemas and Suppositories

Though seldom studied in a formal manner, both enemas and suppositories are widely used in the management of constipation in the elderly. Enemas play an important role in the management and, especially, the prevention of faecal impaction among those at risk. Suppositories can help to initiate and/or facilitate evacuation. For example, an approach that combined daily administration of lactulose with a glycerin suppository and a once-weekly tap water enema was successful in achieving complete rectal emptying and preventing incontinence related to impaction in some institutionalized elderly patients.[113] Similar success rates were obtained using a combination of a laxative and a suppository in stroke patients.[114]

The antegrade continent enema approach involves placing a conduit into the appendix, neoappendix caecostomy or colon to permit the regular instillation of enemas.[115] Some enthusiasm has been expressed for this approach, despite its technical challenges, in patients with intractable slow-transit constipation. When using enemas in any regimen for the treatment of constipation in the elderly, it is necessary to remain mindful of the significant, and even fatal, disturbances of water and electrolyte balance that can occur with use of sodium phosphate enemas in vulnerable patients, such as those with renal impairment and cardiac disease.[116]

7. Summary

Our review of the extant literature reveals a slim evidence base on which to develop a management algorithm for constipation in the elderly. Indeed, it could be said that clinical practice in this area owes more to anecdote than to randomized controlled clinical trials. As a consequence only the following general recommendations can be made:

1. Appreciate the prevalence of constipation in the elderly and, especially, identify those at risk for megacolon and impaction. Prophylactic measures may well be indicated in those at risk for impaction and related incontinence.
2. Search for underlying causes, be they co-morbid diseases or iatrogenic factors. The temptation to regard constipation as an inevitable consequence of aging should be avoided.
3. While institution of dietary and lifestyle measures can be supported on the basis of their general health benefits, evidence for a direct impact of such measures on constipation in the elderly is lacking.
4. In most instances, fibre supplements and simple osmotic laxatives are likely to prove adequate for the relief of symptoms. The clinician needs to be aware of the tolerability and adverse event profile of individual agents in this age group.
5. Notwithstanding the fact that they are widely used in the elderly, treatment with other laxatives in this age group is not supported by evidence from clinical trials. Furthermore, the clinician needs to be constantly aware of the risks of long-term use of laxatives and enemas in this age group and be prepared to review such patients on a regular basis.[117]
6. To date, no safe effective prokinetic agent has been widely approved for the treatment of constipation.
7. The chloride channel agonist lubiprostone shows promise; studies in the elderly are needed.
8. Other approaches, such as biofeedback, may be indicated in certain instances.

8. Conclusion

Constipation is a symptom subject to considerable variation in description and interpretation, and a concise and all encompassing definition of the condition accordingly remains elusive. The subjective nature of the condition must be remembered when

assessing patients of any age with this complaint.[1,18] Regardless of its nature, be it slow-transit or outlet, constipation is a significant healthcare problem in the elderly. There is insufficient evidence to support the use of many commonly used laxatives both in the general population and in the elderly. Lifestyle interventions have value for some patients but data are lacking on the benefits of these interventions in patients with chronic constipation. Management should be tailored to each individual's needs and expectations, regardless of age or place of residence. More elderly individuals should be enrolled in clinical trials.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

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CME

EDUCATIONAL OBJECTIVE: To outline for the internist an approach to the treatment of constipation

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Update on constipation: One treatment does not fit all

ABSTRACT

Constipation is a common clinical problem that can be difficult to manage. It has a variety of identifiable causes, but even idiopathic constipation has different possible mechanisms. Often, the key to improvement and patient satisfaction is to understand the mechanism and the patient.

KEY POINTS

A high-fiber diet often improves functional constipation, but it may worsen slow-transit constipation or dyssynergia (a failure of the pelvic floor muscles to relax). Nevertheless, fiber remains a mainstay of treatment for its ability to provide homogeneous stool consistency.

Drugs approved for treating constipation increase fluid in the lumen, speed intestinal transit, and improve stool consistency, while tegaserod (Zelnorm) additionally acts as a serotonin agonist.

Colonoscopy and other tests are reserved for patients with refractory constipation and those with symptoms suggesting colon cancer.

Prebiotics (short-chain carbohydrates that stimulate activity of beneficial colonic bacterial flora) and probiotics (live bacterial preparations) are under evaluation as treatments for chronic constipation.

Dr. Foxx-Orenstein has disclosed that she has received honoraria from the GlaxoSmithKline and Novartis corporations for serving on advisory committees or review panels.

CONSTIPATION is both a symptom and, when chronic, a multisymptom disorder, and it can overlap with other gastrointestinal tract disorders such as dyspepsia and gastroesophageal reflux disease. Furthermore, one should keep in mind the possibility of cancer and be alert for its warning signs.

Since constipation has a variety of causes and forms, one treatment does not fit all patients. Conservative measures such as recommending that the patient increase his or her intake of dietary fiber and water and engage in more physical activity are still the cornerstone of treatment, but they do not help all patients. On the other hand, polyethylene glycol and stimulant laxatives, which are traditionally given only for a short time, can be safe and effective when given long-term if other agents fail. New agents have become available or are in development.

In this article we outline our approach to constipation, as a guide for internists.

CONSTIPATION IS COMMON, BUT HOW SHOULD WE DEFINE IT?

Constipation affects 2% to 27% (average 14.8%) of the North American adult population—approximately 63 million people.[1] It is more common than many other chronic diseases, including hypertension (48 million people), migraine (33 million), obesity (50 million), and diabetes mellitus (15 million).[1–3]

Constipation affects more women than men (2.1:1 ratio) and more nonwhites than whites (1.68:1).[1] It occurs in all age groups but is more common in those older than 65 years and younger than 4 years.[4,5]

Constipation accounts for more than 2.5 million office visits and more than $500 million spent on laxatives per year.[6,7] Also, people with constipation may report decreased productivity and increased absenteeism.[8]

The broad range in the prevalence of constipation cited above reflects differences in how it is defined and, in particular, a lack of agreement between how patients and physicians perceive it.[1,9] Physicians mainly define constipation on the basis of stool frequency, considering fewer than three bowel movements per week to be abnormal.[1] In contrast, patients typically define it on the basis of bothersome symptoms such as straining, passage of hard stool, unproductive urges, inability to defecate at will, and sensations of incomplete evacuation or abdominal bloating.[1,9,10]

The Rome III diagnostic criteria were developed to provide a consistent diagnostic approach for use in clinical practice and clinical trials.[11] The Rome III criteria define functional chronic constipation as a chronic bowel disorder characterized by two or more of the following:

- Straining
- Lumpy or hard stools
- Sensations of incomplete evacuation
- Sensations of anorectal obstruction or blockage
- Use of manual maneuvers to facilitate defecation (eg, digital evacuation, support of the pelvic floor) during at least 25% of defecations
- Fewer than three bowel movements per week.

Patients tend to define constipation in terms of symptoms, not stool frequency

In addition, loose stools should rarely occur without the use of laxatives, and there should be insufficient criteria for irritable bowel syndrome.[11] Chronicity is established by symptom onset within the previous 6 months and symptom duration of at least 3 months.

In contrast, patients with irritable bowel syndrome, also a functional bowel disorder, experience recurrent abdominal pain and discomfort associated with two or more of the following: symptom improvement with defecation, symptom onset associated with a change in the frequency of bowel movements, and a change in the form or appearance of the stool.

THREE TYPES OF IDIOPATHIC CONSTIPATION

There are three types of primary or idiopathic constipation[5,9,12,13]:

- Functional
- Slow-transit
- Outlet dysfunction.

Functional constipation includes functional chronic idiopathic constipation and constipation-predominant irritable bowel syndrome. It presents with a sense of difficult or delayed evacuation, hard stools, or abdominal bloating or discomfort.[6,9,13] The predominant symptom of constipation-predominant irritable bowel syndrome is severe discomfort or pain; in chronic idiopathic constipation, pain and discomfort may be present but are not the primary symptom.

Slow-transit constipation (or delayed-transit constipation) is associated with a prolonged time between bowel movements. Its symptoms include low stool frequency, lack of urge to defecate, abdominal distention, bloating, and abdominal discomfort.[14]

Outlet dysfunction. Disorders of defecation can be due to mechanical causes such as Hirschsprung disease, anal stricture, cancer, prolapse, and large rectoceles, or from pelvic floor dysfunction. Pelvic floor dysfunction may be due to inadequate or excessive perineal descent or to inadequate propulsive forces, as may occur in neurologic or neuromuscular conditions and dyssynergia.

Pelvic floor dyssynergia, also called anorectal dyssynergia, dyssynergic defecation, and anismus, results from a functional defect in coordinated evacuation. The characteristic symptom is a feeling of being unable to adequately empty the rectum.[14] Other symptoms such as excessive straining and manual disimpaction indicate but are not unique to pelvic floor dyssynergia.[14,15]

Combined forms. Patients may have more than one type of primary constipation and presentation, and pelvic floor dyssynergia has been shown to prolong intestinal transit, which may improve with treatment.

Secondary constipation can be due to causes such as diet, lifestyle, certain medications (calcium channel blockers, beta-blockers, opioids, diuretics, antidepressants, anticonvulsants, antacids, anticholinergics, and antispasmodics),[5,16]

underlying medical conditions (diabetes, hypothyroidism, multiple sclerosis, parkinsonism),[16,17] pregnancy, and advanced age.[18]

NEUROTRANSMITTERS MAY PLAY A ROLE

Among the mechanisms thought to cause chronic constipation are impaired gastrointestinal motility,[19–22] reduced intestinal secretions,[21–23] and inadequate reflex relaxation of the pelvic floor muscles.[22,24]

Neurotransmitters such as serotonin, somatostatin, peptide YY, and vasoactive intestinal peptide affect intestinal secretion and motility.[25,26] Hyperactivity of these neurotransmitters associated with increased secretion and motility results in diarrhea, whereas hypoactivity leads to decreased secretion, delayed transit, and constipation.[23]

Serotonin has a role in regulating visceral pain perception and intestinal motility, as well as secretion.[26–28] Clinical trials have shown that activation of serotonin receptors in the gut enhances gastrointestinal motility, inhibits visceral sensitivity, and stimulates intestinal secretion.[26,27,29]

A hypothesis has recently been proposed that degeneration of enteric neurons may also play a role in the development of severe idiopathic constipation.[30]

DIAGNOSIS IS MOSTLY CLINICAL

The history and physical examination remain the cornerstones in the diagnosis and subsequent treatment of chronic constipation.

History

The history may provide clues as to a primary cause. The patient interview yields information about the frequency and consistency of stool (TABLE 1),[31] the need to strain or manually disimpact, the sense of incomplete evacuation, pain, bleeding, or prolapse.

Risk factors for primary and secondary constipation to note during the interview include age (< 4 years, > 65 years); low-fiber diet; female sex; lack of physical activity; history of childhood constipation, endocrine and neuromuscular disorders, abuse, depression, or anxiety; family history of cancer; and personal history of pelvic surgery.

TABLE 1

The Bristol Stool Form Scale

Type 1	Separate hard lumps, like nuts (hard to pass)
Type 2	Sausage-shaped but lumpy
Type 3	Like a sausage but with cracks on its surface
Type 4	Like a sausage or snake, smooth and soft
Type 5	Soft blobs with clear-cut edges (passed easily)
Type 6	Fluffy pieces with ragged edges, a mushy stool
Type 7	Watery, no solid pieces; entirely liquid

LEWIS SJ, HEATON KW. STOOL FORM SCALE AS A USEFUL GUIDE TO INTESTINAL TRANSIT TIME. SCAND J GASTROENTEROL 1997; 32:920–924.
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Since drugs can also cause chronic constipation, especially in elderly or immobile patients, medication lists should be reviewed and adjustments should be made if necessary (or possible) before recommending laxatives or invasive testing, if no alarm signs are present.

Alarm signs such as weight loss, hematochezia, melena, change in bowel habits, and symptoms refractory to therapy may represent colon cancer and indicate the need for early diagnostic testing.

Signs of cancer: hematochezia, anemia, fecal occult blood, weight loss, fever, nausea, vomiting, acute onset of constipation

Physical examination

Physical examination should always include inspection of the perianal area for evidence of hemorrhoids or fissures. Digital rectal examination may reveal a contracted sphincter or a puborectalis muscle that contracts with the Valsalva maneuver, suggesting dysfunction.

Laboratory testing

If the history and physical examination suggest that the constipation may be secondary, or if the patient is 50 years of age or older, then laboratory studies such as a complete blood cell count, serum electrolyte levels, blood sugar level, and thyroid function studies may help rule out a metabolic, endocrine, or organic cause.

Colonoscopy, other tests

At present, little evidence suggests that routine testing is warranted in patients without

evidence of secondary constipation and without alarm signs. However, diagnostic studies are indicated in patients 50 years of age and older, as well as in those with alarm symptoms such as hematochezia, anemia, a positive fecal occult blood test, unintentional loss of more than 10 pounds, family history of colon cancer or inflammatory bowel disease, fever, nausea, vomiting, acute onset (especially in the elderly), and lack of improvement with conventional therapies regardless of age.[2]

The full length of the colon should be inspected by colonoscopy or by flexible sigmoidoscopy paired with a barium enema study to rule out structural disease. Of note, all patients 50 years of age or older should be screened for colon cancer.

If the patient does not respond to therapy, further tests such as colonic transit studies, anorectal manometry with balloon expulsion, and, possibly, defecating proctography or dynamic pelvic magnetic resonance imaging may be considered. These patients would likely also benefit from referral to a gastroenterologist for further management

Conservative interventions relieve symptoms in a subset of patients with constipation

DIET AND LIFESTYLE AS TREATMENT

For many years, health care providers have provided reassurance and recommended diet and lifestyle modifications as treatment for constipation. Increased water intake, increased activity, and a scheduled attempt at defecation when motor activity in the colon is highest, ie, in the morning or after eating, have all been recommended.

Data on the efficacy of these recommendations are scarce and often contradictory. Studies have shown that increasing water intake or daily exercise is not always helpful.[32–34] Nevertheless, many patients who comply with dietary and exercise recommendations have improvement in symptoms. Eating fewer meals per day (and hence taking in fewer calories) has been shown to be associated with constipation in the elderly. However, no relationships between fiber or fluid intake and constipation were noted.[35]

In a study in which chronically constipated patients were fed a standardized diet that contained 25 g of fiber a day, stool frequency increased significantly and laxative use decreased.[36] While on a high-fiber diet, the patients were divided into two groups, one that drank 1.1 L of fluid per day and one that drank 2.1 L of mineral water per day. Both groups experienced further improvements in stool frequency and decreases in laxative use, with the mineral-water group benefiting the most.[36]

Recently, Murakami and others[37] found, in a cross-sectional study in young Japanese women with low daily fiber intake (6.4 g/day), that low water intake from foods and low magnesium intake were associated with an increasing prevalence of functional constipation as defined by the Rome III criteria. Constipation was also found to be significantly associated with low intake of fruits and vegetables in a study from Singapore.[38]

Moderate physical activity and high fiber intake may be associated with a lower prevalence of constipation in women. In the Nurses' Health Study, more than 62,000 women between the ages of 36 and 61 were surveyed, and those who said they engaged in daily physical activity had a lower prevalence of constipation (prevalence ratio [PR] = 0.56, 95% confidence interval [CI] 0.44–0.70), as did those with a median fiber intake of 20 g/day (PR = 0.64, 95% CI 0.57–0.73).[39]

BULK LAXATIVES (FIBER SUPPLEMENTS): THE FIRST-LINE TREATMENT

Fiber remains the first-line treatment for constipation. It may relieve or improve symptoms in functional constipation. However, fewer than 30% of patients with either slow-transit constipation or pelvic floor dysfunction have improvement in symptoms with fiber, and in these types of constipation it can even worsen symptoms.[40]

There is much confusion about what types of fiber should be recommended and how the various types of fiber perform in resolving constipation.

Insoluble fiber

Insoluble fiber resists bacterial degradation in the colon and can retain more water than soluble fiber can.

Bran 20 g/day increased the frequency of bowel movements by 55%, increased fecal weight by 157%, and decreased intestinal

transit time by 50% in women who had three or fewer bowel movements per week.[41]

Muller-Lissner[42] and others performed a meta-analysis and found that bran (25 g/day) increased stool weight and decreased transit time in both healthy controls and patients with chronic constipation. Yet constipated patients taking bran still had lower stool weights and slower transit times than did healthy subjects.

When bran 20 g/day was compared with placebo in chronically constipated patients, bowel frequency and stool weight increased with both treatments,[43] suggesting that factors other than intake may affect bowel function and transit time. However, bran was more effective than placebo in decreasing oroanal transit time.

Elderly constipated patients who received bran 10 g twice a day had significantly shorter transit times (89 hours vs 126 hours) than did those who received psyllium (a soluble fiber) 6 g twice daily. They also needed less additional laxative.[44]

Soluble fiber

Soluble fiber also affects the bowel habits of both healthy and constipated patients.

Methylcellulose, given to healthy volunteers at a dose of 4 g/day, resulted in statistically significant increases in stool weight, fecal water weight, and fecal solids.[45] In constipated patients, methylcellulose 1 g/day was as effective as psyllium 3.4 g/day at increasing stool frequency, fecal water weight, and fecal solids.[45]

Konjac glucomannan was also shown to significantly increase stool frequency, water weight, and fecal solids.[46]

Psyllium. In a study that randomly assigned 22 patients with chronic constipation to receive either psyllium 5 g twice daily or placebo for 8 weeks, followed by a 4-week washout phase in which placebo was given,[47] those who received psyllium reported significant improvements in stool consistency and pain with defecation, as well as significant increases in both stool frequency (3.8 vs 2.9 per week, $P < .05$) and stool weight (665 g vs 405 g, $P < .05$). However, colonic transit times and anorectal manometric measurements did not differ significantly between those who received psyllium vs placebo.[47]

Fiber may not help everyone

Others have also shown that while fiber may improve stool characteristics, it may not significantly alter the sensorimotor functions of the colon and pelvic floor.

Cheskin et al[48] performed a crossover study in 10 constipated men and women in the community. Patients received either 24 g of psyllium fiber daily or a placebo fiber for 1 month and then crossed over to the other treatment for the next month. The most common cause of constipation in this study was pelvic floor dysfunction. Total gut transit time was significantly increased by psyllium fiber, and there was a trend toward increased stool frequency, demonstrating that psyllium clinically improved constipation. However, pelvic floor dysfunction, as measured by rectal manometry, was not improved.

It may be that only people with normal-transit constipation, not those with underlying slow-transit constipation or pelvic floor dysfunction, are helped by additional dietary fiber. Voderholzer and others[40] studied 149 consecutive patients with chronic constipation and evaluated their response to at least 6 weeks of psyllium (*Plantago ovata* seeds 15 to 30 g/day) by serial symptom measurements, oroanal transit times, and functional rectoanal evaluation with defecography, manometry, and sigmoidoscopy. Of the patients with no evidence of pelvic floor dysfunction or slow-transit constipation, 85% improved. However, 80% of those with slow-transit constipation and 63% of those with pelvic floor dysfunction did not improve with the use of fiber. The authors concluded that it is reasonable to try dietary fiber in patients with constipation and, if no improvement is noted, to then consider further investigation for other subtypes of constipation (ie, slow-transit or pelvic-floor dysfunction).

Approved for constipation: lactulose, polyethylene glycol, lubiprostone, tegaserod

Adverse effects may limit the use of fiber and may differ depending on the type of fiber used. Soluble fiber may be better tolerated, especially in patients with constipation-predominant irritable bowel syndrome.[49] Side effects include the sensation of bloating and distention, excessive gas production, and abdominal cramping.

Our recommendations on fiber

We recommend the following regarding fiber in constipated patients:

- Increase fiber intake from natural foods up to 20 g/day. This increase should be completed over 2 to 3 weeks to minimize adverse effects.
- Consider adding a fiber supplement, such as psyllium, if increasing the intake of natural fiber does not relieve constipation-related symptoms.
- If symptoms persist despite the use of fiber supplements and diet and lifestyle modification, then further structural and functional investigation of the colon (anorectal manometry, colonoscopy, defecography, colon manometry) should be considered.

OSMOTIC LAXATIVES

Osmotic laxatives are molecules that are either not absorbed or poorly absorbed and that draw water into the intestinal lumen to maintain isotonicity between the intestinal contents and the serum. Examples are polyethylene glycol, sodium phosphate (Fleet phosphosoda), magnesium hydroxide, magnesium citrate, the sugars lactulose and sorbitol, and glycerin.

Certain formulations of this class of laxative can cause bloating, diarrhea, electrolyte disturbances, volume overload, or dehydration. These effects limit their use, and these medications should be used with caution in patients prone to renal insufficiency or cardiac abnormalities.

Polyethylene glycol is safe and effective for long-term use

Polyethylene glycol

Polyethylene glycol is an exception. It is not absorbed and lacks electrolytes, making it an attractive option in patients with underlying renal or cardiac dysfunction. In several placebo-controlled trials,[50–52] various formulations significantly increased stool frequency while significantly decreasing straining, use of other laxatives, and colonic transit. No increase in adverse effects was noted compared with placebo.

Compared with lactulose, polyethylene glycol at about 21 g/day significantly increased bowel movement frequency while significantly decreasing the sense of straining with bowel movements and flatus due to laxative use.[51] Both polyethylene glycol and lactulose accelerate colonic transit, although polyethylene glycol does so to a greater extent.[53]

Polyethylene glycol has been safe and effective when used for up to 6 months.[54]

Lactulose and sorbitol

Carbohydrate or sugar-based laxatives, if taken in sufficient doses, have a cathartic effect through two mechanisms: a primary osmotic effect of the sugar itself and a secondary osmotic effect as a substrate for colonic bacteria to cleave to acid metabolites, which exert an osmotic effect in the colon. This secondary effect will be discussed in a later section.

Lactulose and sorbitol are sugars that are poorly absorbed by the intestine. Lactulose has been shown to be more effective than placebo in increasing stool frequency, volume, weight, and consistency in chronically constipated patients.[55] In a head-to-head comparison between sugar laxatives, 70% sorbitol was as effective as lactulose in increasing the frequency of bowel movements, and it was similar in its adverse effects[56]; 70% sorbitol is a cost-effective alternative to lactulose in the elderly nursing home population.[57]

Compared with fiber alone, lactulose use leads to a significantly higher number of bowel movements and better stool consistency.[58] However, when lactulose was compared with a combination of fiber and a stimulant laxative, it was less effective than the combination therapy.[59,60]

Sugar laxatives, while effective, may have dose-limiting or use-limiting adverse effects such as abdominal bloating and flatulence.

Phosphate, magnesium

Sodium phosphate, like polyethylene glycol, is often used as a bowel preparation before colonoscopy, for which it is about as good or slightly better than polyethylene glycol.[61,62]

Although magnesium and sodium phosphate preparations are effective, there are multiple reports of clinically significant electrolyte abnormalities, renal failure, and congestive heart failure occurring with these preparations. Therefore, they must be used with discretion and caution in appropriate patients with frequent monitoring.

STIMULANT (IRRITANT) LAXATIVES

Stimulant laxatives are usually reserved for use when bulking agents and osmotic laxatives

fail. Their mechanism of action involves the alteration of intestinal motility and intestinal fluid secretion.

Anthraquinones (cascara, aloe, and senna), castor oil, and diphenylmethanes (bisacodyl) are the most commonly used stimulant laxatives. They work relatively quickly, often eliciting a bowel movement 2 to 8 hours after they are taken.

This class of laxatives has historically been underused or given for only short periods of time, owing to concern about impairing colonic function, damaging the enteric nervous system, causing laxative dependency, causing cathartic colon, and even causing colon cancer. However, there is very little evidence to support these concerns. Stimulant laxatives can be used on a more regular basis when bulking or osmotic agents fail.[63]

Possibly of greatest concern is the potential for the overuse and abuse of stimulant laxatives. Excessive use can cause electrolyte disturbances brought about by high-volume watery diarrhea. Risk factors for overuse and abuse include underlying psychiatric disturbances and eating disorders. Prescribing other types of laxatives or cathartic agents may reduce risk, but the potential for abuse exists with all categories of laxatives.

TEGASEROD: GONE BUT STILL AVAILABLE, ON A CONTROLLED BASIS

Tegaserod (Zelnorm), a serotonin (5-HT4) agonist, was used predominantly in women with constipation-predominant irritable bowel syndrome and in men and women with chronic constipation. However, it was suspended from the market in the United States in March 2007 owing to concern about a high risk of adverse cardiovascular effects compared with placebo.

In a double-blind, randomized controlled trial, men with chronic constipation who received tegaserod 6 mg twice a day for 12 weeks had more spontaneous bowel movements than those receiving placebo ($P = .04$).[64]

Lin et al[65] evaluated the use of tegaserod 6 mg twice daily for 4 weeks in both men and women with chronic constipation. Those receiving tegaserod had significantly more spontaneous bowel movements per week, less straining, and better stool consistency than those receiving placebo.

Tegaserod can still be obtained for appropriate patients via a treatment investigational new drug application. Safety data are under further review by the US Food and Drug Administration. Studies of other serotonin agonists are under way.

LUBIPROSTONE

Lubiprostone (Amitiza) is an agonist of the chloride channel subtype 2, found on the apical membrane of intestinal epithelial cells. It causes increased chloride secretion into the intestinal lumen, enhancing intestinal fluid secretion. It has been shown to be effective in chronic constipation by improving stool consistency and increasing the motility of the small intestine and colon.[66] It is approved for treating chronic constipation in adults.

In randomized, double-blind trials, patients receiving lubiprostone 24 µg twice daily for 4 weeks had significantly more bowel movements per week, reported significantly better stool consistency and less abdominal bloating and straining, and rated their constipation as less severe than did patients receiving placebo.[67–69]

More recently, in an open-label study, lubiprostone improved constipation symptoms when taken for up to 48 weeks.[70]

The drug is well tolerated, but its adverse effects include nausea (which appears to be dose-dependent and may diminish over time or if the drug is taken with food), diarrhea, and headache.[68] Of note, the drug appears to be well tolerated by older people (65 years of age and older), in whom adverse effects occur less often than in younger users.[71] However, adverse events may cause up to 20% of patients to stop taking the drug.[69] When lubiprostone is discontinued, patients may once again revert to their baseline bowel habit.[72]

Cost may prohibit lubiprostone from becoming a first-line drug for chronic constipation

Lubiprostone has not been compared with conventional laxatives, and cost may prohibit it from becoming a first-line drug for chronic constipation.[73]

OTHER PROMOTILITY AGENTS

Several promotility agents have been studied for treating chronic idiopathic constipation.

Cisapride (Propulsid), a 5-HT3 receptor antagonist and 5-HT4 receptor agonist, and prucalopride, a 5-HT4 agonist, were effective in relieving symptoms associated with chronic constipation.[74–76] However, safety issues (cardiac arrhythmias) necessitated withdrawal of cisapride from the US market in 2000. Prucalopride is undergoing clinical trials.[77]

Renzapride, a mixed 5-HT4 receptor agonist and 5-HT3 receptor antagonist, has been shown to improve stool consistency and to increase colonic transit in patients with constipation-predominant irritable bowel syndrome.[78] Renzapride has been studied in patients with this condition,[78–81] but not in patients with chronic constipation. Renzapride is in phase III clinical development in the United States for treating constipation-predominant irritable bowel syndrome.

EMERGING TREATMENTS

New drugs with novel mechanisms of action are being investigated for the treatment of chronic idiopathic constipation.

Studies are trying to define the role of prebiotics and probiotics

Neurotrophin-3, a neurotrophic factor, modulates the development of the nervous system by regulating the survival and differentiation of nerves.[82] In patients with functional constipation, subcutaneous doses of neurotrophin-3 improved stool frequency, the number of complete spontaneous bowel movements, and stool consistency.[83]

Alvimopan is a selective antagonist of the mu-opioid receptor that is being studied for opiate-related constipation and postoperative ileus.[84,85] Little of this drug is systemically absorbed and it does not cross the blood-brain barrier; thus, it relieves the opiate-related side effects, ie, bloating, abdominal discomfort, and reduced stool frequency, without interfering with the central analgesic effects.

Linaclotide (MD 1100), a poorly absorbed guanylate cyclase agonist, is also being investigated as a treatment for chronic constipation.[86] Linaclotide increases intestinal fluid secretion and transit via stimulation of cyclic guanosine monophosphate production and activation of the cystic fibrosis transmembrane conductance regulator.[86,87] In preliminary studies, linaclotide increased stool frequency and the Bristol Stool Form Scale consistency score (TABLE 1) by increasing intestinal fluid secretion and transit.[86]

Chenodeoxycholic acid is a bile acid that is synthesized from cholesterol.[88] Treatment of constipation with chenodeoxycholic acid has been proposed, given its laxative effect. A study by Bazzoli et al[89] showed increased stool frequency and a decrease in stool consistency in chronic constipation patients given chenodeoxycholic acid 10 mg/kg/day. The main side effect was diarrhea. Chenodeoxycholic acid may be worthwhile in the management of constipation, but more studies are needed.

PROBIOTICS AND PREBIOTICS

The bacteria of the colon influence peristalsis of the colon.[90] Probiotics (live bacterial preparations) and prebiotics (nondigestible preparations that stimulate the growth or activity of beneficial colonic bacteria) have been gaining interest as potential therapies for constipation.[91,92]

Probiotic bacterial preparations are generally composed of strains of *Bifodobacterium*,[93,94] *Lactobacillus*,[95] and combinations thereof, and are available as mixed preparations of multiple bacterial strains of *Lactobacillus*, *Bifodobacterium*, and *Streptococcus* species, such as VSL#3.[96]

Probiotics may help relieve constipation, but their effect may depend on the strain of bacteria used and the population being studied.[97] In a double-blind parallel study in 70 healthy adults, ingestion of 375 g/day of milk fermented with *B animalis* strain DN-173 010 for 11 days reduced colon transit time by 20% from baseline. The effect was more pronounced in women, particularly in those with longer baseline transit.[98]

Lactic acid-producing bacteria are considered commensal organisms with essentially no pathogenic potential.[99] A review of the safety of bifodobacteria and lactobacilli concluded there was no health risk to consumers.[100]

Prebiotics are short-chain carbohydrates such as lactulose that stimulate the activity of beneficial colonic bacteria.[91] They are thought to have a small laxative effect that is likely both osmotic and due to beneficial actions of bacteria for which they are a substrate. Both konjac glucomannan and lactulose, sugar-based laxatives and prebiotics, have been

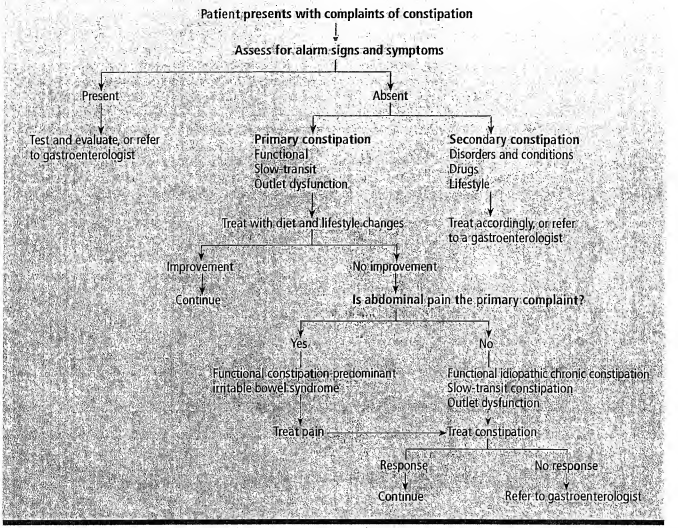

FIGURE 1. Treatment approaches for chronic constipation

shown to significantly increase the fecal concentrations of lactobacilli and total bacteria, possibly through increases in stool bulk.[46] Prebiotics that have been the focus of research include inulin, fructo-oligosaccharides, and galacto-oligosaccharides.[91] Evidence on the efficacy of probiotics and prebiotics at relieving symptoms of constipation, however, is inconclusive because few well-controlled clinical studies have been done.[91,92]

STRATEGIES FOR MANAGING CHRONIC CONSTIPATION

In the absence of secondary causes, treatment of chronic constipation is focused on relieving symptoms.

The first line of treatment includes nonpharmacologic approaches such as increasing fiber in the diet or taking fiber supplements (FIGURE 1). Additionally, lifestyle changes such as increased physical activity and dietary modification, as well as cognitive behavior therapy (biofeedback and hypnosis), may relieve symptoms in a subset of patients with chronic constipation. Although lacking in clinical evidence, milk of magnesia[101] and probiotics are often prescribed.

If symptoms are refractory to these traditional treatments, agents such as lactulose and polyethylene glycol may provide relief.[11,21] Although they do not address the underlying cause of constipation, these agents increase the fluid content of the intestine, contribut-

ing to improved stool consistency, and consequently increase the frequency of bowel movements.

Lubiprostone similarly increases the fluid content of the colon, contributing to improved stool consistency, reduced fecal transit time, and increased frequency of bowel movements.[66,70,102] Unlike lactulose and polyethylene glycol, which are indicated only for short-term use, lubiprostone has been found to be safe and effective when used for up to 48 weeks.[70,71]

Biofeedback is the preferred treatment for pelvic floor dyssynergia, in which it has a success rate of 70% to 81% and in which it is superior to standard treatment (laxatives, fiber, and education).[103–105] In an instrument-based training program, patients receive auditory or visual feedback or both to help train the pelvic floor and relax the anal sphincter while simulating defecation. It also improves rectal sensation to assist in proper evacuation. The best outcomes are achieved when committed patients receive instruction from empathetic, properly trained physical therapists or other technicians. Studies show that the benefits of biofeedback are long-lasting.[104] It does not improve slow-transit constipation, though pelvic floor dyssynergia and slow-transit constipation can overlap. ■

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2. Publication No.: 0891-1150
3. Filing date: 10/01/08
4. Issue frequency: Monthly
5. No. of issues published annually: 12
6. Annual subscription price: $108.00
7. Complete mailing address of known office of publication: Cleveland Clinic Journal of Medicine, 9500 Euclid Avenue, NA-32, Cleveland, OH 44195.
8. Complete mailing address of headquarters or general business office of publisher: Cleveland Clinic Journal of Medicine, 9500 Euclid Avenue, NA-32,Cleveland, OH 44195. Contact person: Peter G. Studer, Publisher. Telephone: 216-444-1155.
9. Full names and complete mailing addresses of publisher, editor, and managing editor: Peter G. Studer, Publisher, Cleveland Clinic Journal of Medicine, 9500 Euclid Avenue, NA-32, Cleveland, OH 44195; Brian F. Mandell, MD, PhD, Editor-in-Chief, Cleveland Clinic Journal of Medicine, 9500 Euclid Avenue, NA-32, Cleveland, OH 44195; Ray Borzacchiello, Managing Editor, Cleveland Clinic Journal of Medicine, 9500 Euclid Avenue, NA-32, Cleveland, OH 44195.
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social adjustment to whatever degree of dysfunction they may exhibit will be facilitated by our own better understanding of the subtle and protean role of sexuality in the modern world.

PROSTIGMIN ASSESSMENT TEST OF FERTILITY IN SPINAL MAN

By Sir LUDWIG GUTTMANN and Dr. J. J. WALSH
National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury, England

SINCE Spellanzani's observations on the copulative posture of the spinal frog (1768) the patho-physiology of the sexual function in the spinal man both in animals and man has been a subject of clinical observations and physiological research (Tarchanow, 1887; Thorburn, 1888; Bernhardt, 1888; Wagner & Stolper, 1898; Sherrington, 1906; Riddoch, 1917; Foerster, 1936). However, it is only during the last 20 years or so that as a result of the greatly increased survival rate of patients with spinal cord injuries, comprehensive studies on potency and fertility in the spinal man have been undertaken. Investigators have employed various procedures to assess potency and fertility in these patients which can be divided into two main groups.

A. Questionnaire and Personal Interview Techniques

The investigators have, of course, to rely entirely on the statements of the individual by these techniques. Results obtained with these methods, were reported by Bors, in 1948 on 157 and 1963 on 529 patients, Talbot in 1949 on 208 and in 1955 on 408 patients, Zeitlin *et al.* in 1957 on 100 and Tsuji *et al.* in 1961 on 655 patients. The latter authors stressed the difference between results obtained with the questionnaire technique and personal interview by finding a higher percentage of erections and ejaculations recorded by the personal interview technique. However, there is general agreement amongst all these authors that the percentage of erections 52-94 per cent. were infinitely higher than that of the ejaculations 3-19·7 per cent. Intercourse possibility was 23-33 per cent., orgasm 6-14 per cent. and reproductive results were the lowest (up to 5 per cent.). Bors (1963) stated that while erection is more frequent with high lesions, ejaculation occurs more often in those with low lesions. This is not, as will be shown later, in accordance with our experience.

B. Direct Examination of the Ejaculate obtained

1. **By Prostatic Massage.** This technique was used by Horne, Paul and Munro (1948). These authors found that the amount of ejaculate by prostatic massage could be increased with prior electric rectal stimulation, a method which was previously employed by Dexter, Lerner and Kaplan (1940) and by Joel (1941). However, Bors and co-workers were not impressed by the results obtained with this method in their own cases which was in accordance with Kuhn's findings (1950).

2. By Testicular Biopsy. Bors and co-workers studied biopsy specimens from testes in 34 patients with spinal cord injuries. They found that in all but three cases the biopsy revealed tubular atrophy while there was no disturbance of Leydig cells. Furthermore, with two exceptions, they found a correlation between testicular biopsy findings and the level of the spinal cord lesion. Lesions at or below T11 showed a lesser degree of testicular abnormalities. The authors also correlated the biopsy findings with the result of sweat tests using the Quinizarin method (Guttmann, 1937-47) and thus were able to study the relationship between testicular function and other components of the autonomic system. With four exceptions, a close relationship was found between testicular biopsy findings and the result of the sweat test. Lesser testicular changes were associated with normal sweating while major testicular abnormalities were associated with impaired sweating. However, the four exceptions showed that there may be dissociation between these two components of the autonomic system. The disdavantage of testicular biopsy is that, from obvious reasons, it cannot be considered as a routine method in these patients and moreover it cannot give any indication of the function of the genital organs as a whole nor does it give any indication of volume, sperm concentration, sperm motility and percentage of normal and abnormal forms.

3. By the Intrathecal Prostigmin Assessment Test. Since the discovery of a selectively stimulating action of prostigmin following intrathecal injection on the reproductive organs of the spinal man by one of us (L. G.) in 1947 this test was employed systematically ever since to assess the potentialities of erections and fertility in paraplegics and tetraplegics. It was found that as a rule a dosage of 0·3 mg. was sufficient to elicit erections and ejaculations in these patients who hitherto had been thought impotent and infertile. This exquisite stimulating effect of the intrathecal prostigmin on the genital organs is in amazing contrast to its depressant effect on the skeletal spastic muscules, the latter previously described in cerebral hemiplegic patients by Kremer and Wright (1941). This depressant effect on spastic skeletal muscles was confirmed in spinal cord lesions as shown in Table I. This effect is in striking contrast to the stimulating effect of this drug on the muscular system following intramuscular injections as found in myasthenia gravis. Furthermore, the intrathecal prostigmin affects, in the great majority of patients, bladder retention for several hours.

Some of our results on the reproductive function on smaller numbers of patients have been previously described in detail (Guttmann, 1953, 1960). The present paper deals with a report on 134 patients with cord or cauda equina lesions at levels ranging from C5 to S4 in whom 180 tests were carried out. One hundred and two patients had complete and 32 incomplete lesions, of whom 104 showed spasticity of various degrees and 30 were flaccid. The average age of the patient was about 28, the youngest being 18, the oldest 47. All patients were in satisfactory general condition at the time of the test and free from infected sores, but the majority had some infection of the urinary tract.

TABLE I

Effect of Intrathecal Prostigmine on Reflex Function

INDICATIONS

The initial test was carried out to determine spermatic abnormalities, as it is well known that reduction of sperm concentration and reduced motility play an important role in male infertility. Both married and unmarried patients in the

TABLE I

Effect of Intrathecal Prostigmine on Reflex Function

Case	Lesion	Reflex function before injection						Reflex function at time of ejaculation or at height of effect on motor function					
		K.J.		A.J.		P.R.		K.J.		A.J.		P.R.	
		R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.
1	C7 Complete	−	+	+	+	→	→	−	−	−	+	→	→
2	T5 Complete	+	+	+	+	←	←	−	−	−	−	←	←
3	T6 Complete	+	+	+	+	→	→	−	−	−	−	→	→
4	T6/7 Complete	+	+	+	+	←	←	−	−	−	−	←	←
5	T6/7 Complete	+	+	+	+	←	←	−	−	−	−	←	←
6	T7 Complete	+	+	+	+	←	←	−	−	−	−	←	←
7	T7 Complete	+	+	+	+	←	←	−	−	−	−	←	←
8	T7 Complete	+	+	±	−	←	←	−	−	−	−	←	←
9	T9 Complete	+	+	+	+	←	←	−	−	−	−	←	←
10	T10 Incomplete	+	+	+	+	←	→	+	+	+	+	→	→
11	T10 Complete	+	+	+	+	←	←	+	−	+	−	←	←
12	T10 Complete	+	+	+	+	←	←	+	−	+	−	←	←
13	T11/12 Complete	+	−	+	+	(←)	←	−	−	−	−	(→)	→
14	L1/L2 Complete	−	+	−	+	−	←	−	−	−	−	−	−
15	L1/L3 Complete (Spastic)	−	+	+	+	←	←	−	−	−	−	−	−
16	L2 Complete (Spastic)	+	+	+	+	←	←	−	−	−	−	−	−
17	L5 Complete	+	−	−	−	−	←	−	−	−	−	−	−
18	S1 Incomplete	+	+	−	−	−	→	−	−	−	−	−	−
19	S2 Incomplete	+	+	+	−	→	→	−	−	−	−	−	−

great majority are naturally very interested in their chances of reproductive activity. This information was found to be sometimes particularly important in the cases of the Catholic faith or those who were engaged to Catholic girls.

Repeated tests were carried out, (1) to check the motility and concentration of sperms and their cytology, (2) to repeat the test with a higher dosage when the first test revealed a negative result (in a few of the patients the dosage had to be increased to 0·5, 0·7 and even 1 mg.), (3) to check motility concentration and differential cytology following hormone treatment, (4) for the purpose of artificial insemination.

METHODS AND DOSAGE

Because of certain undesirable side-effects, especially vomiting, the patient has to refrain from solid food for some hours before the test, and for three hours before injection the patient should not take anything by mouth. Before the test a full neurological examination of the lower limbs is carried out and full assessment of reflexes and muscle tone has to be made. This is of special importance in more distal cord lesions as there are often mixed forms of spasticity and hypo- or areflexia in certain parts of the lower limbs. This is particularly apparent in transverse lesions below T10/11, where the injury may also affect the conus and epiconus, or in higher transverse lesions which are combined with longitudinal damage.

Procedure. The patient is prepared in the usual way for a lumbar puncture and the test is carried out in a separate room. The drug used was neostigmine methyl sulphate (prostigmin-Roche), made up in 1-cc. ampules each containing 0·5 mg. and a clearly marked 2-cc. syringe is essential for the accurate amount of prostigmin injected.

After lumbar puncture (carried out in lateral position) the Quechenstedt test is carried out to ascertain the presence of absence of a suparachnoid block as this has some bearing on the dosage. If there is no or only a partial block, 0·3 mg. prostigmin is injected after first withdrawing 1-2 cc. C.S.F. into the syringe to mix with the prostigmin. In high thoracic and cervical injuries it is safer to start with 0·25 mg. because of the rise in blood pressure in these high lesions during ejaculations as a result of powerful contractions of the seminal vesicles and other ejaculatory organs, which may set up the same autonomic hyperreflexia as described previously by the forceful contraction of bladder and other internal organs (Guttmann & Whitteridge, 1947; Guttmann, 1954, 1969). If there was a complete block, 0·3 to 0·5 mg. was injected. In some cases where the initial test was negative and especially if the neurological examination indicated little or no effect on muscle tone and reflexes, the test was repeated using larger doses of prostigmin provided there had been no untoward side-effects during the original injection. Up to 1·5 mg. prostigmin has been given in one exceptional case of conus-cauda equina lesion. After injection the needle is withdrawn, a dressing applied and the patient turned on his back with a pillow under his head. A glass container of a suitable size with a wide screw-cap is given to the patient with instructions to observe any erections and obtain any semen ejaculated. The examination of reflexes and muscle tone in the lower limbs is carried out repeatedly after the injection and recorded every ½-1 hour as this gives a good indication of the effect of prostigmin in each individual case. In distal lesions with areflexia this information is, of course, not obtainable. It is also important to measure pulse and blood pressure regularly during the test,

especially in high thoracic and cervical lesions because of the possibility of exaggerated autonomic hyperreflexia due to seminal contraction during ejaculation. Moreover, in high thoracic and in particular cervical lesions a cystometrogram some time prior to the prostigmin test may give a clue about the degree of irritability of the autonomic system.

RESULTS

The depressant effect on reflex function of the skeletal muscles started as a rule between 15 and 20 minutes after intrathecal injection, but there was as a rule a considerable delay—one to three hours—before the onset of erections and ejaculations which usually occurred at the height of the reflex depression. Once an

TABLE II
Prostigmine Test

				Positive		Negative	
Spastic 104 (77·6%)	Complete	75	(72·1%)	44	(59·7%)	31	(40·3%)
	Incomplete	29	(27·9%)	23	(79·3%)	6	(20·7%)
Flaccid 30 (22·4%)	Complete	27	(90%)	9	(33·3%)	18	(66·7%)
	Incomplete	3	(10%)	2	(66·7%)	1	(33·3%)
Total 134		134		78	(58·2%)	56	(41·9%)

erection had started it continued in most of the cases for a considerable time, either intermittently or continuously and sometimes it persisted for hours even after emissions occurred. In two low thoracic lesions (T10 and T12) and one conus lesion, ejaculations occurred without erections. The number of ejaculations varied considerably from patient to patient and also in different tests in the same patient. Only the minority of patients produced a single emission and as many as seven or more were observed in some patients within a period of two hours. Table II shows number and percentage of positive ejaculations results in our 134 patients. 59·7 per cent. of the 70 complete and 75·4 per cent. of the incomplete spastic lesions showed positive results, while in 66·7 per cent. of the complete flaccid lesions no ejaculations occurred. As will be seen in Table III the majority of negative results occurred in lesions at levels between T10 and L4.

The volume of the ejaculated seminal fluid varied considerably from patient to patient and also in different tests on the same patient. In those cases who had several ejaculations the volume of each emission became progressively less. However, sometimes the second or third emission was found to be larger than the first. This may be accounted for by the fact that in these cases there had been no ejaculation for very long periods before the tests and it would appear that in some of them accumulated stimuli were necessary to set the whole mechanism of ejaculation into action.

No relationship was found between volume and sperm concentration in the

TABLE III
Prostigmine Test

					Positive	Negative
Cervical (7·46%)	10	Complete	Spastic	3	1	2
			Flaccid	1	...	1*
		Incomplete	Spastic	6	6	...
			Flaccid	...	...	...
T1-T6 (22·38%)	30	Complete	Spastic	25	20	5
			Flaccid	2	1	1
		Incomplete	Spastic	3	3	...
			Flaccid	...	...	...
T7-T9 (22·38%)	30	Complete	Spastic	19	14	5
			Flaccid	1	...	1
		Incomplete	Spastic	9	5	4
			Flaccid (Polio)	1	1	...
T10-T12 (31·34%)	42	Complete	Spastic	19	7	12
			Flaccid	12	3	9
		Incomplete	Spastic	10	8	2
			Flaccid	1	1	...
L1-L4 (11·97%)	16	Complete	Spastic	8	2	6
			Flaccid	8	3	5
		Incomplete	Spastic	...	...	...
			Flaccid	...	...	...
L5-S4 (4·47%)	6	Complete	Spastic	1	...	1
			Flaccid	3	2	1
		Incomplete	Spastic	1	1	...
			Flaccid	1	...	1
Total	134			134	78	56

* Alcohol Block

TABLE IV
Level of lesion | Dose

various subjects or in repeated tests on the same subject. Considerable variations were found and the ejaculate may be just prostatic fluid with complete aspermia. Conversely, a small volume of seminal fluid may contain a much higher sperm concentration than a large volume.

TABLE IV

Name	Age	Date of test	Level of lesion: Comp.	Level of lesion: Incomp.	Spastic	Flaccid	Dose prostig-mine mg.	Result emission	Volume cc.	Count mill.	Motility per cent	Differential count
Sturg.	32	9.11.48	–	T12	+	–	0·4	1 – (Urine) 2 – (Urine) 3 – (Urine) 4 + 5 + + + 6 + + + 7 +	– – – 1·0 1·1 1·2 0·7	– – – 87 51 58 41	– – – 44 42 37 33	73% abnormal 14% immature
Fro.	29	10.9.48	S1	–	–	+	0·5	1 + 2 + + + 3 + + + + 4 + + + + 5 + + + 6 + + + 7 +	1·0 1·1 0·9 0·5 0·5 0·3 0·3	4·5 3·1 2 2·3 0·95 0·6 0·56	23 20 17 18 11 9 5	Squamous cells + + + + + + Testicular cells Testicular cells Testicular cells Debris Debris Debris
Harv.	27	2.2.48	C7/T1	–	+	–	0·3	1 + + + 2/3 + + + 4/5 + + + 6 + +	1 2 0·5 0·5	73 57 23 15	2 4 20 20	Pus cells Pus cells & R.B.C. Pus cells & R.B.C. Pus cells & R.B.C.
Morg.	37	8.1.48	–	C6	+	–	0·3	1 + 2 + +	1·5 1·7	45 46	66 30	– – – –
Craw.	23	12.10.56	T7	–	+	–	0·4	1 + + + 2 + + + 3 + + + 4 + + + 5 + +	5·0 2·5 1·5 5 < 1	100 100 50 25 nil	10% (5%) weak	–

Negative
2 1*
5 1
5 1 4
12 9 2
6 5
1 1 1
56

erable variations
plete aspermia.
h higher sperm

The percentage of viable motile sperms was, as a rule, well below normal, especially in complete lesions, but in a small number of patients there were 50 per cent. and more of viable sperms. Table IV demonstrates the results obtained in five patients complete and incomplete, of various level who during the test had more than one emission. It is known from fertility tests in normal subjects that, although a high motility of sperms is an essential property of fertile spermatozoa, the ratio of motility provides only a rough index to the viability of the sperm population and its suitability for fertilising the ovum.

TABLE V

Comparative Microscopic Results of Seminal Fluid in Two Prostigmine Tests
Cauda Equina Lesion (incomplete) below L5

Specimen	Volume		Count (millions, 1cc)		Motility	
	13.2.48 c.c.	5.10.48 c.c.	13.2.48	5.10.48	13.2.48 per cent.	5.10.48 per cent.
1	0·5	1·0	11	50	5	70
2	0·5	1·0	12	49	10	70
3	0·5	5·0	111	116	40	50
4	4·5	1·0	90	57	40	50
5	1·0	1·0	122	47	30	40
6	0·5	2·0	142	3·6	30	20

Differential count: 13.2.48

Specimen 1 : 50% abnormal forms (some tailless, some with two heads)
Specimen 6 : 40% abnormal forms (some tailless, some with two heads)

Differential count: 5.10.48

Specimen 3 : Head abnormalities = 49%
Middlepiece and Tail abnormalities = 26%
Total abnormalities = 55%
Specimen 4 : Head abnormalities = 36%
Middlepiece and Tail abnormalities = 29%
Total abnormalities = 65%

Considerable variations were also found on detailed cytological examination in the percentage of normal and abnormal forms of sperms and other cells. The following case (case 17, Table I) may serve as an example of detailed cytological examination, the more so as a comparison is possible between two tests carried out in this patient.

This patient was wounded in June 1944, and sustained incomplete Cauda Equina lesion below L5. He had cordotomy in October 1944, because of pain in right leg. There was recurrence of pain after three weeks although less severe. He had erections and nocturnal emissions three months after injury, but lost emissions after cordotomy. He has spontaneous erections and is able to walk. First intrathecal prostigmin test 17.2.48, 0·3 mg. Second test 5.11.48, 0·3 mg. He had six emissions on each occasion.

Table V shows the comparative microscopic results of seminal fluid in the

two tests. Table VI shows six patients with negative results in repeated tests in spite of increased dosage. It may be noted, however, that in particular one single negative result does not necessarily signify permanent infertility as improvement of reproductive function is possible. Actually the prostigmin test may act as an induced stimulus on the function of the reproductive organs. Three of our patients with negative results became fathers later, one, an incomplete lesion below T_7, even of twins. Although from obvious reasons some scepticism may be justified in such cases, the possibility of such achievement cannot be ruled out.

It has already been mentioned that one of the reasons for the prostigmin test is to use the seminal fluid obtained for artificial insemination at the patient's request who failed to get ejaculations during intercourse. The first four cases have been reported previously (Guttmann, 1961). They were all unsuccessful. However, the cause may not have been in all four cases necessarily with the paraplegic male. In one of the cases examination of the wife revealed an uterus bicornis and in another the wife was suffering from inflammation of the cervix. In 10 more cases artificial insemination was since carried out by one of us (J. J. W.). In two cases the wives conceived but in one abortion took place after three months and in the other after five months. No information is available about the gynaecological condition of the wives of these patients. Table VII gives information about the number of artificial inseminations carried out in five cases and the findings of the seminal fluid. However, that this method can be used successfully has been shown by Dr. R. Spira (1956), whose paraplegic patient, a complete 7th thoracic lesion, fathered a child after three unsuccessful attempts by assisted insemination with the help of the intrathecal prostigmin test. This case also shows that improvement of fertility is possible in the paraplegic. Spira's patient was treated with Testosterone, 25 mg. daily for 14 days and Gonadotrophin 1000 units daily for four weeks. We also have given hormonal treatment combined with vitamin E 20 mg. three times daily and in certain cases with weak erections with Potensan (Medo) 2-3 pellets, two to three times daily. Although we have seen definite improvement of fertility our results do not allow definite conclusions.

Side-effects on Autonomic Mechanisms. This paper should not be completed without mentioning some undesirable side-effects of prostigmin on the cardio-vascular system and other components of autonomic mechanisms. Headaches, sweating and vomiting may occur regardless of the lesion, and if vomiting becomes more marked it may counteract the stimulating effect on the reproductive organs. It can be controlled by 1/100 Atropine. Only in three cases it was thought wise to give an intravenous drip of saline to prevent dehydration. It has already been mentioned that in cord lesions above T_5 and in particular cervical lesions, violent contractions of the ejaculatory organs can set up exaggerated autonomic hyperreflexia with considerable rise of systolic and diastolic blood pressure and in one case with complete tetraplegia below C7 the initial blood pressure of 90/70 rose during the ejaculatory stage of the test to 230/150. Immediate application of Pentolonium (Ansolysen) intravenously reduced immediately the paroxysmal hypertension. It may be noted that in this case a previous cystometrogram revealed a very irritable discoordinated automatic bladder and an infusion of only 50 cc. of fluid into the bladder elicited repeated and most powerful detrusor contractions. Therefore, it may be useful to carry out a cystometrogram prior to the prostigmin test in high cord lesions to ascertain the degree of irritability of autonomic

TABLE VI

Name	Age	Date of test	Level of lesion		Spastic	Flaccid	Dose prostigmine (mg.)	Result
			Comp.	Incomp.				
Vid.	21	22.5.63 13.6.63	T6	—	—	+	0·4 0·5	— —
Att.	43	3.10.66 31.10.66 29.11.66	T10	—	+	—	0·25 0·37 0·75	— — —
Crock.	22	27.7.64 21.9.64	—	T10	+	—	0·3 0·5	— —
All.	30	5.4.62 2.5.62 20.11.62	—	T11	±	—	0·3 0·5 0·75	— — —
Win.	25	8.9.60 6.10.60 2.11.60	T12	—	+	—	0·3 0·5 0·75	— — —
Holl.	30	29.7.63 24.1.64	L1/3	—	±	—	0·3 0·6	— —

TABLE VII

Name	Age	Date of prostigmin	Level				Dose	Result No. of emissions	Total sperm	Motility per cent	Pus cells	Insemi-nation	Result insem.
			Comp.	Incomp.	Spastic	Flaccid							
Den.	28	10.4.69		C.6	Yes		0·25						

Holl.	30	29.7.63 24.1.64	L1/3	—	±	—	0·3 0·6	— —

TABLE VII

Name	Age	Date of prostigmin	Level				Dose	Result No. of emissions	Total sperm	Motility per cent	Pus cells	Insemination	Result insem.
			Comp.	Incomp.	Spastic	Flaccid							
Den.	28	10.4.69		C.6	Yes		0·25	+3	100 m. 60 m. 25 m.	<5 16 20	RBC +++ no significant growth	+	—
		30.6.69		C6	Yes		0·25	+3	175 m. 100 m. 100 m.	15(10 sl) 15(10 sl) 15(5 sl)			
Cor.	30	12.4.65	T5		Yes		0·3	+2	45 m.	6		+	—
		11.6.65	T5		Yes		0·3	+2	50 m.	5		+	—
		12.10.65	T5		Yes		0·4	+2	not reported	<5 sl. active	+++	+	?3/12 abortion correspondence
		11.7.66	T5		Yes		0·45	+2	100 m.	10		+	—
		18.10.66	T5		Yes		0·4	+2	70 m.	7		+	
		24.2.67	T5		Yes		0·4	+1	?	?		+	—
		19.6.67	T5		Yes		0·4	+2	?	?		+ with Dutch cap	—
Sym.	28	18.11.66		T6	Yes		0·25	+3	50 m.	10	+++	+	—
		11.2.67		T6	Yes		0·25	+5	45 m.	40	+++	+	—
		19.9.67		T6	Yes		0·25	+4/5	40 m.	20	+	+	—
Elm.	36	19.5.66	T7		Yes		0·3	—					
		7.11.67	T7		Yes		0·4	+1	some motile	(10) sl.	—	+	—
		24.10.68	T7		Yes		0·4	+3	65 m.	1	sterile	+	—
Reev.	29	3.3.56	T7		Yes		0·5	+4	330 m.	75 abnormal 9 active	+		
	38	9.8.65	T7		Yes		0·45	+2	200 m.	20 fully 10 slightly		+	—
		10.1.66	T7		Yes		0·45	+3	50 m.	5 slightly		+	—
		2.5.66	T7		Yes		0·25	+3	½ m.	10			

mechanisms. Cerebral haemorrhages due to exaggerated autonomic hyperreflexia have been reported in the literature following bladder distension and during the last stages of labour in high lesions. We lost one tetraplegic with a complete C6/7 lesion. He had his first prostigmin test on 2.2.48 when following injections of 0·3 mg. the initial blood pressure rose from 120/85 to 150/90. Apart from vomiting, which was controlled by 1/100 Atropine, there were no undesirable side-effects during three ejaculations. He got married and in 1961 he asked for a prostigmin test for the purpose of artificial insemination. This was carried out on 15.9.61. One and a half hours following injection of the same doses as previously (0·3 mg.) he developed an epileptic fit and died later as a result of a cerebral ventricular haemorrhage. At post-mortem also an undiagnosed abscess behind the pancreas was found.

Summary

1. The widespread belief that patients with severe injuries of the spinal cord are completely and permanently impotent and infertile is no longer valid.

2. The distinct stimulating effect of intrathecal prostigmin on the sexual organs has opened new possibilities for clinical, physiological and biochemical research in a field where imaginative speculation and deduction on scanty grounds rather than on well-founded evidence have prevailed.

3. A variety of types and degrees of reproductive deficiency can be distinguished by the intrathecal prostigmin test.

4. Future research on the chemistry of the seminal fluid may give clues to abnormalities of the morphology and function of semen.

5. The intrathecal prostigmin test can be utilised for artificial insemination. It is essential that the female partner should undergo a thorough gynaecological and biochemical examination including pH of vaginal and cervical secretion and assessment of the most suitable time for assisted insemination.

6. Blood pressure and pulse should be examined at regular intervals during the prostigmin test from the start, especially in lesions above $T_5/6$ to counteract excessive autonomic hyperreflexia by appropriate measures (Ansolysen, etc).

7. Patients, especially those with higher lesions should be warned about undesirable side-effects of prostigmin.

Résumé

1. La croyance que les malades avec des lésions sévères de la moëlle épinière en ce qui concerne leur impotence complète et permanente, ainsi que leur manque de fertilité n'est plus maintenant valide.

2. L'effet stimulant sur les organes génitaux de la prostigmine intrathécale a ouvert de nouvelles possibilités de recherches cliniques, physiologiques, et biochimiques, là la spéculation et la déduction sur un terrain fragile plutôt que sur des évidences a prévalu.

3. Les variétés de types, de degrés de déficiences reproductives ont pu être distinguées par le test à la prostigmine.

4. A l'avenir, des recherches sur la biochimie du sperme pourra donner des indications sur la fonction et la morphologie anormale des spermatozoïdes.

5. Les tests à la prostigmine peuvent être utilisés pour l'insémination artificielle. Il est indispensable que la partenaire soit examinée d'une façon gynécologique sérieuse et que le moment le plus favorable pour l'insémination soit relevé.

6. La tension artérielle et le pouls doivent être examinés à des intervalles réguliers pendant le test à la prostigmine depuis le début, surtout en ce qui concerne les lésions au-dessus de D5, D6, de façon à lutter contre une hyper-réflectivité autonome exessive.

7. Les malades, surtout ceux avec des lésions hautes, doivent être avertis des effets secondaires indésirables de la prostigmine.

Zusammenfassung

1. Die allgemeine Ansicht, dass Patienten mit schweren Rückenmarksläsionen völlig und dauernd impotent sind, ist nicht mehr haltbar.

2. Der ausgesprochen stimulisierende Effekt von Prostigmin auf die sexuellen Organe hat neue Möglichkeiten für klinische, biochemische und physiologische Untersuchungen in einem Gebiet eröffnet, wo bisher Spekulation und Deduktion an Stelle von klarem Beweis überwogen hat.

3. Verschiedene Typen und Grade sexueller Insuffizienz können durch den subarachnoidalen Prostigmintest ermittelt werden.

4. Zukünftige Untersuchungen der chemischen Zusammensetzung des Semen könnten Aufschluss über seine Morphologie und Funktion geben.

5. Der Prostigmintest kann für artifizielle Insemination verwandt werden. Eine genaue gynäkologische Untersuchung einschliesslich Bestimmung des besten Zeitpunkts für die Insemination is notwendig.

6. Blutdruck und Puls muss regelmässig während des Prostigmintests gemessen werden, besonders in Läsionen oberhalb T5, um gesteigerte autonomische Hyperreflexie durch geeignete Mittel (Ansolysen) auszuschalten.

7. Patienten, besonders solche mit Zervikalläsionen, sollen über mögliche unerwünschte Seiteffekte unterrichtet werden.

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SEXUAL FUNCTION AND DYSREFLEXIA

By A. B. Rossier, W. H. Ziegler, P. W. Duchosal and J. Meylan[1]

In a previous paper (Rossier *et al.*, 1969), we have presented the case history of the successful delivery of a tetraplegic patient who showed symptoms of autonomic dysreflexia during labour. There were hypertension and bradycardia but no

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Paraplegia 21 (1983) 30–36

TREATMENT OF ANEJACULATION IN THE TOTAL PARAPLEGIC BY SUBCUTANEOUS INJECTION OF PHYSOSTIGMINE

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Summary. The authors describe a new therapy for paraplegic anejaculation.

Sub-cutaneous injection of Physostigmine with certain precautions and with selected methods of application can be used for patients where there is the same indication for the use of an intrathecal injection of Neostigmine. The T12–L2 myelomeres must be intact. The new treatment is easier to perform, and when the patient has experimented with three tests in our hospital without any problems, he is granted permission to apply this treatment at home, without any medical supervision.

Key words: Paraplegic; Ejaculation; Physostigmine—subcutaneous injections.

Introduction

IN 1949, Guttmann described a new way to treat paraplegic anejaculation: intraspinal injection of neostigmine (ISN) (Guttmann, 1949). Several studies have been carried out since then including attempts to assess paraplegic fertility (Guttmann & Walsh, 1971), to define as precisely as possible the indications of this technique (Chapelle *et al.*, 1974). Other types of treatment have been described in order to avoid the most important side effect of the technique, that is, Autonomic Hyperreflexia (AHR), including electric masturbation (Tarabulcy, 1972) or electro-ejaculation provoked by an intrarectal probe (François *et al.* 1978).

This work was undertaken in an attempt to find a pharmacological agent which would replace ISN; which would be easier to administer and and which would have no side effects.

Working Hypothesis

Neostigmine is an indirect parasympathomimetic agent which reversibly antagonizes acetylcholine esterase. Since it does not cross the blood brain barrier, it must be administered *in situ* by lumbar puncture to produce ejaculation. Physostigmine is also a reversible acetylcholine esterase antagonist, but it can transverse the blood brain barrier, and can thus be administered parenterally, for example by subcutaneous injection. However the general parasympathomimetic effect of the drug becomes a problem. By analogy, with the treatment of parkinsonism, it seemed logical to

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administer at the same time an inhibitor of the peripheral parasympathetic system (or its peripheral effectors). N-buthylhyocine bromide was used for this purpose, thus permitting the central action of physostigmine, whilst eliminating its disagreable peripheral effects (nausea, vomiting).

The subjects chosen were men between 18 and 50 years of age with traumatic paraplegia present for at least six months (in order to assure neurological stabilisation), with a clinical syndrome of complete spinal cord section. Patients who had undergone treatment which would affect the neuro-muscular urogenital system, even temporarily, were excluded from the study.

Method

A clinical neurological examination, described in detail elsewhere (Grossiord *et al.*, 1978) was performed to determine the extent of the syndrome, affecting both the somatic (cerebrospinal) and vegetative (ortho and parasympathetic, in the anatomical sense) systems (Chapelle, 1978).

Every patient was initially treated with physostigmine (PSC).

Several weeks later the same patients received either intraspinal neostigmine (especially when the first treatment failed), or a second dose of physostigmine (especially when the first treatment was successful). As we have previously shown, ISN can only be effective when the T12, L1 and L2 myelomeres are not involved. (Chapelle, 1974; Chapelle, 1982). We did not systematically perform the ISN test when the lesion affected segments T12, L1 or L2 and the PSC test was negative. Patients were required to fast for at least 12 hours, and have an empty bladder.

In the ISN test, after lumbar puncture was done, 0·25 or 0·5 mg of neostigmine were mixed with cerebrospinal fluid and injected intrathecally; masturbation began 30 minutes later.

In the PSC test, 2 mg of physostigmine sulfate was injected subcutaneously 30 minutes after N-buthylhyocine 40 mg was given. Masturbation began 15 minutes later. If no result was obtained, some patients received a supplementary injection of 1 mg of physostigmine 30 minutes after the first injection. If side-effects appeared during the ISN or PSC test, the patient was asked to stop masturbation. After verification that the bladder was empty, metoclopramide (10 mg) was injected subcutaneously, (sometimes in association with an intravenous injection of 0·25 mg atropine).

The PSC test was always performed by the same nurse who was uninformed as to the nature of the product injected for the result expected *a priori*, but who told the patient that every test would be successful. This precaution seemed to be a non-neglibible criterion of good faith in the experiment which the nurse fully accepted.

The tests were considered positive if ejaculation occurred and spermatozoa were present in the ejaculate.

Results

The results are summarized in Table I. The first PSC test was successful in five of the 20 patients. Three patients (numbers 7, 8 and 15) were successful in subsequent tests. Twelve remained unsuccessful.

Department of Veterans Affairs

JRRD Volume 41, Number 1, Pages 53–58
January/February 2004
Journal of Rehabilitation Research & Development

Effects of neostigmine and glycopyrrolate on pulmonary resistance in spinal cord injury

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Abstract—Preliminary findings in subjects with spinal cord injury (SCI) suggest that neostigmine administered intravenously increases colonic tone, increases colonic contractions, and facilitates bowel evacuation. Of concern are potential pulmonary side effects, including an increase in airway secretions and bronchospasm. The objectives of the study were to determine the effects of intravenously administered neostigmine or neostigmine combined with glycopyrrolate on forced oscillation indices in persons with SCI. Pulmonary resistances at 5 Hz (R5) and 20 Hz (R20) were measured with the use of an impulse oscillation system (IOS) in 11 subjects with SCI. Values were obtained before and after the intravenous administration of 2 mg of neostigmine alone and, on a separate day, before and after the administration of 2 mg of neostigmine combined with 0.4 mg of glycopyrrolate. Baseline R5 and R20 values before neostigmine correlated significantly with baseline values before neostigmine combined with glycopyrrolate. Following neostigmine, mean R5 values increased 25% and mean R20 values increased 18%. Following neostigmine combined with glycopyrrolate, mean R5 values fell 9% and mean R20 values fell 7%. In summary, baseline IOS values obtained on 2 different days were highly reproducible in this population. Neostigmine alone induced significant bronchoconstriction, whereas neostigmine combined with glycopyrrolate caused bronchodilation.

Key words: glycopyrrolate, impulse oscillation, neostigmine, spinal cord injury.

INTRODUCTION

Neostigmine, an acetylcholinesterase inhibitor, has been used successfully to rapidly decompress the colon in patients with acute colonic pseudo-obstruction [1]. Preliminary findings in subjects with spinal cord injury (SCI) suggest that parenteral administration of the drug increases colonic tone, increases colonic contractions, and facilitates bowel evacuation [2]. Side effects are of concern because in some individuals, the agent increases airway secretions and bronchial reactivity, which may exacerbate active bronchospasm [1]. These concerns may be particularly significant in subjects with tetraplegia, who demonstrate hyperresponsiveness to methacholine, histamine, and ultrasonically nebulized distilled water

Abbreviations: COPD = chronic obstructive pulmonary disease, IOS = impulse oscillation system, Rrs = respiratory system resistances, SCI = spinal cord injury, sGaw = specific airway conductance, VA = Department of Veterans Affairs.

This material was based on work supported by the Department of Veterans Affairs (VA) Rehabilitation Research and Development Center for Excellence on the Medical Consequences of SCI.

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comparable to that seen in mild asthma [3–5]. Also, individuals with tetraplegia have reduced baseline airway caliber caused by unopposed parasympathetic activity, thereby suggesting that any agent that increases acethylcholine concentrations at muscarinic receptors may cause further bronchoconstriction [6]. One potential method for attenuating the effects of neostigmine on pulmonary function without reducing bowel stimulation is the simultaneous administration of the anticholinergic agent glycopyrrolate. To assess the effects of neostigmine alone and neostigmine combined with glycopyrrolate on pulmonary function in SCI, we used the impulse oscillation system (IOS) to measure total respiratory system resistances over a wide range of frequencies. Values at lower frequency (R5) estimate central and peripheral pulmonary mechanics; values at high frequency (R20) reflect more central airway dynamics.

METHODS

Subject Selection

Eleven subjects participated in the study. Three had chronic cervical cord injury (tetraplegia) and eight had thoracic or lumbar injuries (paraplegia). All were outpatients followed by the SCI Service at the Department of Veterans Affairs Medical Center, Bronx, New York (BVAMC). All participants were clinically stable and denied any history of asthma, allergies, recent respiratory tract infections, or other acute pulmonary conditions. The Institutional Review Board of the BVAMC approved the study, and we obtained informed consent prior to investigation. All subjects were being studied primarily so that we could assess the value of neostigmine in facilitating bowel evacuation. None of the subjects were using medications known to affect airway tone or responsiveness.

Equipment

We measured total pulmonary resistances using a commercially available system (VIASYS Healthcare, Respiratory Technologies, Yorba Linda, California). While subjects were supine, measurements were obtained with the use of nose clips and a free-flow mouthpiece. Subjects were asked to slightly extend their necks and to limit abdominal motion during the study. A laboratory technician supported the subjects' cheeks during the maneuver. The forced oscillation instrument applied pressure pulses five times/second during tidal volume breathing. We calculated resistances from the pressure/flow relationship obtained from impulses applied at the mouth during a 30 s period and analyzed them at 5 and 20 Hz (R5 and R20). We repeated 30 s recordings until three recordings fulfilled quality assurance coherence coefficient criteria. A test was accepted if the coherence coefficient was 0.7 or greater at 5 Hz and 0.9 or greater at 20 Hz for either five breaths or 30 s of recording [7]. Large and small airway mechanics were inferred from responses at high (20 Hz) and low (5 Hz) frequencies, respectively. Low frequency oscillations are transmitted to the lung periphery, while those at 20 Hz are limited to larger airways [7].

Study Protocol

On study day 1, baseline measurements at R5 and R20 were obtained. The measurements were repeated 30 minutes after the intravenous administration of 2 mg of neostigmine. On a separate day, within 2 weeks of the first study, R5 and R20 were measured before and after the intravenous administration of 2 mg of neostigmine combined with 0.4 mg of glycopyrrolate.

RESULTS

Morphometric data are listed in **Table 1**. Three subjects had tetraplegia and eight had paraplegia with levels of injury ranging from C-4 to L-3. Eight were never smokers and three were ex-smokers. Baseline R5 and R20 values before neostigmine and before neostigmine plus glycopyrrolate are shown in **Table 2**. Following administration of neostigmine mean R5 and R20 values increased by 25 and 18 percent, respectively (**Table 2** and **Figure 1**). On a separate day, following the administration of neostigmine combined with glycopyrrolate, mean R5 and R20 values decreased by 9 and 7 percent, respectively. Baseline R5 and R20 values obtained for individual subjects were found to be highly correlated on 2 separate days of testing (**Figure 2**).

DISCUSSION

We used IOS to measure total pulmonary resistance, which is the composite of chest wall, pulmonary tissue, and airway resistances. Body plethysmography would have been more sensitive and specific for assessing airway

Table 1.
Characteristics of subjects.

Subject	Age	Height	Weight	DOI	LOI	Group	Motor COL	Smoke History
1	48	70	165	14	C4	Tetraplegia	Complete	Never
2	29	65	150	5	C5–6	Tetraplegia	Complete	Never
3	49	72	156	31	C6–7	Tetraplegia	Incomplete	Former
4	52	69	200	8	T3	Paraplegia	Complete	Never
5	25	68	140	1	T3	Paraplegia	Incomplete	Never
6	39	71	205	2	T6	Paraplegia	Complete	Former
7	46	71	228	17	T7	Paraplegia	Complete	Never
8	40	69	183	15	T9–11	Paraplegia	Complete	Former
9	42	73	205	21	T11	Paraplegia	Complete	Never
10	42	74	270	16	T12	Paraplegia	Complete	Never
11	57	68	150	17	L-3	Paraplegia	Incomplete	Never
Mean	43	70	187	13	—	—	—	—
SD	9	3	40	9	—	—	—	—

COL = completeness of lesion DOI = date of injury LOI = level of injury

Table 2.
IOS results before and after neostigmine and neostigmine +glycopyrrolate.

Subject	R5 Neostigmine			R20 Neostigmine			R5 Neostigmine +Glycopyrrolate			R20 Neostigmine +Glycopyrrolate		
	Before (kPa/L/s)	After (kPa/L/s)	% Change	Before (kPa/L/s)	After (kPa/L/s)	% Change	Before (kPa/L/s)	After (kPa/L/s)	% Change	Before (kPa/L/s)	After (kPa/L/s)	% Change
1	0.339	0.558	65	0.303	0.407	34	0.363	0.379	4	0.321	0.330	3
2	0.387	0.398	3	0.271	0.330	22	0.359	0.311	−13	0.278	0.222	−20
3	0.559	0.616	10	0.397	0.375	−6	0.503	0.428	−15	0.349	0.375	7
4	0.715	0.893	25	0.573	0.681	19	0.850	0.820	−4	0.644	0.648	1
5	0.279	0.287	3	0.226	0.235	4	0.275	0.275	0	0.235	0.227	−3
6	0.376	0.637	69	0.271	0.459	69	0.411	0.361	−12	0.318	0.279	−12
7	0.540	0.629	16	0.308	0.327	6	0.631	0.441	−30	0.356	0.328	−8
8	0.364	0.407	12	0.261	0.280	7	0.364	0.333	−9	0.259	0.228	−12
9	0.461	0.604	31	0.329	0.378	15	0.465	0.417	−10	0.399	0.342	−14
10	0.692	0.865	25	0.509	0.540	6	0.672	0.612	−9	0.509	0.446	−12
11	0.732	0.864	18	0.543	0.679	25	0.678	0.653	−4	0.514	0.505	−2
Mean	0.495	0.614	25	0.363	0.426	18	0.506	0.457	−9	0.380	0.357	−7
SD	0.163	0.201	23	0.124	0.150	20	0.178	0.168	9	0.126	0.132	8

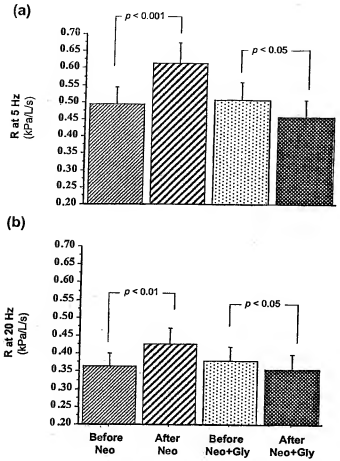

Figure 1.
(a) R5 and **(b)** R20 values before and after administration of neostigmine (neo) alone or before and after neostigmine combined with glycopyrrolate (gly). Data are expressed as mean ± SD. An unpaired Student's *t*-test was applied to determine differences for R5 and R20 for neostigmine alone and for neostigmine combined with glycopyrrolate.

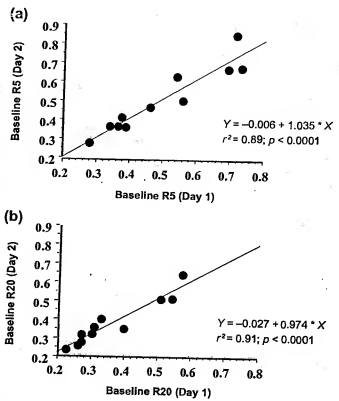

Figure 2.
Correlation of baseline **(a)** R5 values on days 1 and 2 and **(b)** R20 values on days 1 and 2. Simple regression analysis was used to assess the relationships between **(a)** days 1 and 2 of baseline R5 values and **(b)** days 1 and 2 of R20 values.

resistance, but this modality was not practical in the current study. The IOS has significant advantages, in that the equipment is portable and tests can be performed at the bedside during normal tidal breathing with minimal patient effort. Because of low reproducibility and wide range of normal values, IOS has been suggested to have limited utility [8]. However, in the current study, although baseline values varied widely among the different subjects, baseline R5 ($r^2 = 0.89$) and R20 ($r^2 = 0.91$) had significant reproducibility in individual subjects studied on two separate days spanning a several-week period. This high reproducibility suggests that many of the variables, which may affect oscillation measurements, including state of relaxation, position of arms, and tongue position, are better controlled when measurements are obtained in the supine position.

In the current study, the intravenous instillation of neostigmine was followed by a significant increase in R5 (25%) and R20 (18%). Comparable increases in both parameters indicate that the agent induced significant constriction of both small and large airways. Although subjects with tetraplegia and paraplegia had similar responses to neostigmine, only three subjects with tetraplegia were studied. Previous observations showing that subjects with tetraplegia, but not those with paraplegia, were hyperresponsive to aerosolized methacholine and that they had reduced baseline specific airway conductance (sGaw) suggest that individuals with higher-level lesions would be more susceptible to the bronchoconstrictive effects of neostigmine [3,6]. A significant increase in airway resistance has been reported in able-bodied individuals following neostigmine [9]. Bronchospasm and

tracheobronchial hypersecretion have been observed in patients undergoing reversal of neuromuscular blockade with neostigmine combined with an anticholinergic agent [10,11].

We found that administering neostigmine combined with glycopyrrolate was followed by significant bronchodilation as measured by decreases in R5 (9%) and R20 (7%). These findings demonstrate that bronchoconstriction associated with neostigmine is prevented by the simultaneous administration of an anticholinergic agent, without decreasing the effectiveness of neostigmine on bowel evacuation [2]. We did not evaluate the effect of glycopyrrolate alone on IOS parameters. By using neostigmine and atropine combined to reverse neuromuscular blockade in patients with or without chronic obstructive pulmonary disease (COPD), Bourgain et al. found that total respiratory resistance was not altered significantly and that changes were similar in COPD compared with normals [12]. Other investigators, by use of spirometry or body plethymography, have shown that intravenously administered or nebulized glycopyrrolate caused significant bronchodilation in normal subjects and among patients with COPD or asthma [13–17].

CONCLUSION

In summary, in subjects with SCI, the intravenous infusion of neostigmine was associated with a significant increase in total pulmonary resistance. The combination of neostigmine with glycopyrrolate was associated with a significant decrease in resistances, demonstrating that cholingerically mediated bronchoconstriction is prevented by the addition of glycopyrrolate.

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Submitted for publication August 8, 2003. Accepted in revised form November 5, 2003.